AWARD NUMBER: W81XWH-10-1-1024

TITLE: Diagnosis of Compartment Syndrome Based on Tissue Oxygenation

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REPORT DATE: June 2015

TYPE OF REPORT: FINAL

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
June 2015	FINAL	09/30/2010 - 03/29/2015

4. TITLE AND SUBTITLE
Diagnosis of Compartment Syndrome Based on Tissue Oxygenation

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-1024

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Northern California Institute for Research and Education
San Francisco, CA. 94121-1545

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The diagnosis of acute compartment syndrome (CS) remains problematic due to difficulty in diagnosis. Current treatment for acute extremity symptomatic CS is fasciotomy. However, surgical treatment has associated morbidity and may delay the recovery of the patients. Continuous measurement of intramuscular tissue oxygenation (PmO2) of the leg has been shown to be feasible in humans and highly responsive to induced compartment syndrome and fasciotomy in a dog model. Using the same model, we investigated the relationship between PmO2 and tissue viability. We further tested the feasibility of non-surgical treatment of compartment syndrome using phenylephrine and dobutamine in the dog model. Under general anesthesia, CS was induced in the anterolateral compartment of one hindlimb via Hespan infusion. Polarographic oxygen probes were placed percutaneously into the anterolateral compartment. Compartment pressure, diastolic blood pressure and tissue oxygenation (PmO2) was recorded every 30 seconds. In the treated group, pharmacological treatments begin at 1 hour after the compartment syndrome is induced. Infusion of intravenous phenylephrine was initiated at 25mcg/min and titrated up to 100mcg/min as needed to increase the diastolic blood pressure 30mmHg above the baseline. Intravenous dobutamine at 60mcg/min was initiated 2 hours later. Six to seven hours after treatment, fasciotomy was performed on one leg. Animals were euthanized 2 weeks postoperatively at which point muscle biopsies were performed. Tissue viability was assessed MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Pharmacological treatment significantly increased PmO2 in the anterior compartment muscle. Two weeks after surgery, there was no significant difference between pharmacological treated and pharmacological plus fasciotomy treated groups. However, either treated group has a significantly higher tissue viability compared to the non-treated group ($P<0.01$). This result suggests that keeping the blood pressure at a high level using pharmacological agents may serve as an alternative to surgical treatment for acute compartment syndrome.

15. SUBJECT TERMS
compartment syndrome, diagnosis, muscle tissue oxygenation, muscle tissue viability, treatment

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	**45**	**19b. TELEPHONE NUMBER** *(include area code)*

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1. INTRODUCTION

The subject of this research is acute extremity compartment syndrome. Compartment syndrome describes the elevation of pressure within the fascial compartments of the extremities, leading to compromise of circulation, ischemia, and necrosis. Treatment is immediate fasciotomy to relieve pressure because delay can have devastating consequences. Delayed fasciotomy has been reported to have high rates of muscle excision, amputation, and mortality in combat casualties evacuated from Iraq and Afghanistan. Difficulty in diagnosis is the major reason why compartment syndrome remains a problematic area of orthopaedic trauma. Because the pathophysiology is pressure-induced ischemia, i.e., lack of oxygen, monitoring tissue oxygenation as a strategy for diagnosis makes good intuitive sense. Direct measurement of tissue oxygenation in skeletal muscle with a minimally invasive probe is feasible and responsive to changes in oxygenation. The purpose of this study is to investigate continuous measurement of tissue oxygenation in muscle as a method for identifying acute compartment syndrome and guiding treatment in the well-established dog infusion model. The scope of the research includes determining feasibility for warning criterion for compartment syndrome based on tissue oxygenation; threshold times and values of tissue oxygenation for irreversible muscle necrosis; and potential efficacy of nonsurgical treatments to increase peripheral oxygen delivery and compare to fasciotomy. The study was performed in 3 phases. In all phases, compartment syndrome was induced with infusion of fluid into the anterolateral compartment of the hind limb while the dog is under anesthesia. Tissue specimens were harvested 2 weeks later for quantitative analyses of muscle necrosis. In Phase 1, compartment syndrome and tourniquet ischemia were induced to varying degrees of severity, followed by fasciotomy or release of tourniquet, and correlated with degree of necrosis. In Phase 2, compartment syndrome was induced based on tissue oxygenation without fasciotomy and correlated with degree of necrosis. In Phase 3, nonsurgical treatment (phenylephrine and dobutamine) was administered and the tissue oxygenation response and necrosis were compared with fasciotomy.

2. KEYWORDS

acute compartment syndrome, fasciotomy, tissue oxygenation, compartment pressure, skeletal muscle, ischemic necrosis, dog model, extremity trauma, polarographic oxygen probe

3. OVERALL PROJECT SUMMARY:

- **What were the major goals of the project?**

Specific Aim #1: Develop warning criterion based on PmO2 by comparing tissue oxygenation and pressure in compartment syndrome of known severities.

Specific Aim #2: Compare the response of tissue oxygenation to ischemia induced by compartment syndrome to ischemia induced by tourniquet.

Specific Aim #3: Determine threshold times and values of tissue oxygenation during compartment syndrome for reversible and irreversible muscle necrosis.

Task 1. Performance of Phase 1 experiments. (completed 2/11/2013)

Specific Aim #4: Validate tissue oxygenation by inducing compartment syndrome of varying severity based on tissue oxygenation and comparing the degree of necrosis with the amount predicted based on Specific Aim 3.

Task 2. Performance of Phase 2 experiments. (completed 5/23/2013)

Specific Aim #5: Investigate the effectiveness of nonsurgical treatments for compartment syndrome compared to fasciotomy.

Task 3. Performance of Phase 3 experiments. (completed 10/28/2013)

- **What was accomplished under these goals?**

1) Major activities

All 3 phases were completed. Animals underwent experiments under general anesthesia. The investigators were assisted by veterinarians who managed intraoperative care including anesthesia, post-operative care including pain control, housing, and euthanasia. Animals were premedicated with 0.2 mg/kg acepromazine and 0.05 mg/kg atropine. Anesthesia was induced with 20 mg/kg of propofol and maintained with 1-5% inhaled isoflurane. Compressed air was used to ventilate the animals. Animals remained under anesthesia for the duration of the experiment. An arterial line was placed for continuous monitoring of blood pressure and intravenous access was maintained for intraoperative monitoring and infusion of medications and fluids. A warming blanket was placed on the animal to maintain the core temperature. This experiment was conducted under the approval of the Institutional Animal Care and Use Committee of ISIS Services, LLC (San Carlos, CA).

In legs undergoing compartment syndrome, this was induced in the anterolateral compartment of the lower hindlimb. An 18 gauge IV was introduced into the midsubstance of the muscle at the midpoint between the proximal and distal ends at the midpoint between the anterior and posterior ends. Hydroxyethyl starch colloid fluid, chosen because of convenient storage and same osmolality as plasma, was infused into the muscle through the 18 gauge IV using gravity of the height of the fluid bag. Infusion continued until the target compartment pressure was achieved and maintained for a goal duration of 8 hours.

In legs undergoing tourniquet ischemia, a tourniquet was placed over the ipsilateral thigh and inflated to 300 mmHg to produce ischemia in the anterolateral compartment of the lower hindlimb.

Muscle tissue oxygenation (partial pressure of oxygen, or PmO2) was continuously monitored with use of a tissue oxygenation probe (Licox, Integra Lifesciences). The probe was placed using the modified Seldinger technique with an 18 gauge IV needle within the muscle substance of the anterolateral compartment of the lower hindlimb at the same location in all animals using anatomic landmarks. Compartment pressure (CP) was monitored using a straight needle connected to an arterial line manometer. This has been shown to be an accurate technique though with a positive bias of approximately 22mmHg (Boody JBJS 2005). Therefore, the observed CP was adjusted downward by 22mmHg. The 14 gauge IV needle was inserted in similar fashion as the tissue oxygenation probe. PmO2 was recorded every 30 seconds and CP every 2 minutes and were continuously recorded for 1 hour after fasciotomy or tourniquet release.

Postoperatively, animals were given 0.1 mg/kg buprenorphine subcutaneously for analgesia. Animals were monitored daily for signs of pain and distress and analgesics were adjusted for adequate pain control by the attending veterinarian. On postoperative day 14, animals were euthanized using intravenous overdose injection of sodium pentobarbital and

bilateral thoracotomy. Immediately after euthanasia, the anterolateral compartment muscle tissue was harvested bilaterally for histologic and biochemical examinations. Biopsy specimens were 0.5 cm diameter x 1 cm length.

In terms of compartment pressure, severity of compartment syndrome is measured by absolute compartment pressure (CP) or perfusion pressure, i.e., the difference between diastolic blood pressure and compartment pressure (DBP-CP). The perfusion pressure is called "ΔP," and a lower number denotes less perfusion pressure, i.e., more severe compartment syndrome. A ΔP value that is negative indicates a severe condition in which the compartment pressure is higher than the diastolic blood pressure. The CP and ΔP values were adjusted by 22mmHg from the actual measurements as described above.

The phases were completed as follows:

Phase 1 (n=16): Compartment syndrome was induced and maintained in one leg for up to 7.5 hours in four degrees of severity, followed by fasciotomy.

1) Low severity (n=4): ΔP>20mmHg, i.e., compartment pressure is at least 20mmHg lower than diastolic pressure
2) Medium severity (n=5): ΔP is 10-20mmHg
3) Medium-High severity (n=2): ΔP is 0-10mmHg
4) High severity (n=4): ΔP is <0, i.e., the compartment pressure is equal to the diastolic pressure

In the contralateral leg of the same animal, tourniquet ischemia of four durations was induced, followed by tourniquet release:

1) Low severity (n=4): 2 hours
2) Medium severity (n=4): 4 hours
3) Medium-High severity (n=4): 6 hours
4) High severity (n=4): 8 hours

The presence and extent of change in PmO2 was observed during compartment syndrome and tourniquet ischemia. For 1 hour following fasciotomy/release of the tourniquet, the recovery or lack of recovery of tissue oxygenation after relief of the ischemia was observed. The final tissue oxygenation was correlated with tissue viability.

Phase 2 (n=8): Compartment syndrome was induced and maintained to a goal tissue oxygenation, as opposed to Phase 1 where a goal compartment pressure was used. In contrast to Phase 1, fasciotomy was not performed. The achieved compartment syndrome PmO2 in each leg was categorized into 4 groups:

1) Low severity (n=3): PmO2>10mmHg,
2) Medium severity (n=5): PmO2>5,<10mmHg
3) Medium-High severity (n=3): PmO2>2,<5 mmHg
4) High severity (n=5): PmO2<2mmHg

Compartment syndrome was maintained for 7-8 hours. The final PmO2 at the time of compartment syndrome was correlated with tissue viability of specimens harvested from the same muscle 2 weeks later.

Phase 3 (n=8): Compartment syndrome was induced with high severity (CP>70mmHg). Phenylephrine was administered intravenously at 25 ug/min one hour after inducing compartment syndrome. Phenylephrine flow rate was increased to 100 ug/min until the target pressure in the anterolateral compartment was reached (the compartment pressure made equal to the diastolic pressure). Dobutamine was administered intravenously at 60 ug/min two hours after the phenylephrine. After 6-8 hours of compartment syndrome, 6 legs underwent fasciotomy. The remaining 10 legs did not. Tissue viability of specimens harvested 2 weeks later was compared between the fasciotomy and non-fasciotomy legs as well as with the results of Phase 2 (no fasciotomy and no phenylephrine or dobutamine).

Euthanasia was performed 2 weeks after completion of the procedures because this is the duration necessary for the degree of muscle viability or necrosis to become apparent on histology. Previous studies lack direct quantitative measurement of muscle necrosis, and this represents a gap in current knowledge. Because accurate determination of the degree of necrosis is crucial, muscle viability was evaluated using three independent quantitative methods:

Tissue viability index ("TVI"): Tissue viability was measured with a previously validated colorimetric assay [1]. This assay is based on the conversion of a colorless MTT substrate (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into a purple formazan product by mitochondrial enzymes active in living tissue. Muscle biopsies (5 mm) were taken from the proximal, medial, and distal sections of the left and right tibialis anterior (TA) of the anterolateral compartment of each animal. Biopsies were also taken from the left and right quadriceps of each animal to serve as uninjured control muscle. The muscle pieces were diced, incubated in MTT solution, and washed in isopropanol overnight at 37°C to dissolve the colored product into solution. The muscles were removed from the isopropanol dried overnight at 60°C. Optical density (OD) of the isopropanol was measured at 570 nm and normalized to the dry weight of the muscle. The tissue viability index (%) was calculated as the ratio between the TA muscle (average OD of the proximal, medial, and distal portions) and the quadriceps of each animal. A higher TVI indicates higher viability.

Histologic injury severity score ("HIS"): Muscle sections were mounted onto cork disks with 10% w/v tragacanth gum and flash-frozen in liquid nitrogen-cooled isopentane. The blocks were sectioned into 12 μm slices with a Microm HM550 cryostat (Thermo Scientific, Waltham, MA). Sections were taken of blocks from proximal, medial, distal areas of both the left and right TA, as well as from the left and right quadriceps. Slides were visualized on a Zeiss Axiovert 200M inverted light microscope (Carl Zeiss Microscopy, Jena, Germany) at 200X magnification and images captured with a Canon digital camera.

Cryosections were stained with hematoxylin and eosin (H&E) to visualize cell morphology and damage. Damage scores were assessed for the medial portion of each animal's left and right TA. Cells were considered damaged when observed to have irregular borders, abnormally small size, irregular shapes, or inconsistent texturing (discounting freezing and sectioning artifacts) as per established standards . Percentage of total damage was measured as the number of damaged myocytes per total myocytes counted [2]. A higher HIS indicates lower viability.

Percent fibrosis ("fibrosis"): To visualize fibrosis, slides were stained with a Masson's Trichrome kit (American MasterTech, Lodi, CA). Fibrosis was quantified as the amount of

collagen per total area of the sample field. For the score of each TA, three areas of the medial section were scored and their scores averaged. Each image was scored by two independent reviewers which were averaged. All histological quantification was performed with Image J® software (National Institutes of Health, Bethesda, MD) [3, 4]. A higher percent fibrosis indicates lower viability.

2) Specific objectives

The work focused on the priority research area of preventing, identifying, and treating compartment syndrome. The objective of this study was to investigate continuous measurement of tissue oxygenation in muscle as a potentially rapid, objective, and physiologic method for the identification of acute compartment syndrome. It was based on the sound rationale that the pathophysiology of compartment syndrome is ischemia induced by pressure. Measurement of tissue muscle oxygenation is a novel use of an existing technology that appears uniquely well-suited for this application. Work by other investigators has established the suitability of this probe for muscle ischemia, and a pilot study showed it to be feasible in humans. A closely related objective was the investigation of vasoactive medications as possible alternative treatment to fasciotomy. We utilized an animal model with remarkable translational potential for humans and a probe and medications that have are FDA approved with proven safety profiles. We studied muscle tissue oxygenation during experimental compartment syndrome under controlled conditions in a well-established large animal model.

3) Significant results or key outcomes

We accomplished the largest animal study utilizing a large animal model in the body of scientific literature for acute extremity compartment syndrome. We utilized the same animal model and similar experimental techniques and survival time as the classic studies that form the foundation for current clinical practice. Those historical dog studies established the threshold values for absolute compartment pressure and ΔP that are applied to human patients today. We utilized multiple modern quantitative, validated, and reproducible techniques to measure tissue viability which distinguishes our study from the previous literature. These considerations lend our findings substantial validity with a high probability of acceptance by the orthopaedic trauma community.

Summary statistics were calculated for each leg due to the large amount of data collected for each leg. For each leg undergoing compartment syndrome, mean absolute compartment pressure was determined during compartment syndrome ("CS CP") and post-fasciotomy ("postCS CP") which were recorded at identical time points with corresponding measurements of PmO2 (i.e., CP and PmO2 data were collected at identical time points for identical durations). ΔP was calculated at each time point as the difference between absolute CP and diastolic blood pressure (mm Hg) and the mean ΔP during CS was calculated (CS ΔP). Negative values indicate compartment pressure exceeding diastolic blood pressure (i.e., larger negative values indicate more severity).

Pre-tourniquet PmO2 ("preTI PmO2") and pre-compartment syndrome PmO2 ("preCS PmO2") are the mean PmO2 for 10 minutes preceding induction of tourniquet ischemia and compartment syndrome, respectively. PmO2 during tourniquet ischemia ("TI PmO2") is the mean PmO2 starting at tourniquet inflation and ending at tourniquet deflation. PmO2 during

compartment syndrome ("CS PmO2") is the mean PmO2 starting at infusion for induction of compartment syndrome and ending at fasciotomy.

Post-tourniquet PmO2 ("postTI PmO2") is the mean PmO2 starting at tourniquet deflation and ending upon removal of the tissue oxygenation probe. Post-fasciotomy PmO2 ("postCS PmO2") is the mean PmO2 starting at fasciotomy and ending upon removal of the tissue oxygenation probe.

Two definitions for severe ischemia based on PmO2 were utilized: PmO2<1mmHg and ≤0. The aggregate times of TI PmO2 and CS PmO2 during which PmO2 was less than 1mmHg and less than or equal to 0mmHg were calculated for each leg.

In addition, for each leg, severity of experimental ischemia (tourniquet ischemia and compartment syndrome) in terms of PmO2 was represented by a Riemann sum calculated as the difference between mean TiPmO2 (or CS PmO2, when applicable) and preTI PmO2 (or preCS PmO2), multiplied by the duration of TI (or CS), therefore yielding mmHg*minutes. Larger negative values indicate more severity (i.e., larger decreases from preTI and preCS PmO2 for longer durations).

For each leg undergoing compartment syndrome in Phase 1, postCS PmO2 was compared to preCS PmO2 by calculating the absolute difference (mmHg) between the two means and the ratio of mean post:pre PmO2.

In the same fashion as for PmO2 describe above, for each leg, severity of compartment syndrome in terms of CP was represented by a Riemann sum calculated as CS CP minus preCS CP multiplied by the duration of CS (mmHg*minutes); higher positive values indicate more severity. Severity of compartment syndrome in terms of ΔP was represented by a Riemann sum calculated as CS ΔP minus preCS ΔP multiplied by the duration of CS (mmHg*minutes); larger negative values indicate more severity.

a) Phase 1 significant results and key outcomes

Tourniquet ischemia

Tissue oxygenation measurements reflected the underlying changes in tissue oxygenation as the tourniquet was applied and released. There was a significant difference between preTI PmO2 and TI PmO2 (38.26→1.41 mmHg, p<0.001 by Wilcoxan ranked sums test for paired non-parametric data) and TI PmO2 and postTI PmO2 (1.41→40.14 mmHg, p<0.001).

Tourniquet time was significantly negatively correlated with viability as measured by TVI (p=0.004, Pearson=-0.702). However, there was no significant correlation between tourniquet time and postTI PmO2 (p=0.46). Because greater than 6 hours of warm ischemia is widely viewed as a clinically important threshold, the Medium-High and High severity groups were combined for data analysis: <3 hours, 4 hours, and >6 hours. There were significant differences in TVI among the three degrees of severity (p=0.04 by Kruskal-Willis test). Tourniquet time exceeding 6 hours had a mean TVI of 0.70. There was a negative correlation between TVI and severity of tourniquet ischemia as represented by duration of PmO2<1mmHg, though this did not reach statistical significance (p=0.06). There was no significant correlation with PmO2≤0mmHg (p=0.3).

Recovery of postTI PmO2 to preTI PmO2 was significantly associated with the degree of tissue viability. Following release of tourniquet pressure, 8 animals had a mean postTI PmO2 equal or greater than mean preTI PmO2, and 7 animals had mean postTI PmO2 lower than preTI PmO2. Animals with postTI PmO2 that was equal or greater than preTI PmO2 had significantly higher TVI than postTI PmO2 that was less than preTIPmO2 (89.11% vs. 73.90%, $p<0.05$ by Mann-Whitney test).

There was no significant correlation detected between postTI PmO2 and TVI ($p=0.09$) nor between postTI-preTI PmO2 difference and tissue viability ($p=0.5$). There was no statistically significant difference detected in TVI using values of PmO2 that have been proposed as thresholds for tissue viability: recovery to 50% of preTI PmO2 ($p=0.06$) or PmO2>10 mmHg ($p=0.1$). Severity of tourniquet ischemia as measured by mmHg*minutes difference from preTI PmO2 did not significantly correlate with viability ($p=0.1$).

Compartment syndrome

Data from one animal (Experiment #1) was not used because of technical problems obtaining accurate PmO2 and CP; results are based on the remaining 15 animals. We confirmed our hypothesis that tissue oxygenation measurements reflected the underlying changes in tissue oxygenation as compartment syndrome was induced and then treated by fasciotomy. There was a significant difference between preCS PmO2 and CS PmO2 (32.12→3.82 mm Hg, $p\leq0.001$) and CS PmO2 and postCS PmO2 (3.82→47.15 mm Hg, $p\leq0.001$). There was a significant difference between CS CP and postCS CP (61.82→13.54 mm Hg, $p<0.001$) as well as CS ΔP and postCS ΔP (-5.58→38.88 mm Hg, $p<0.001$), which demonstrates that fasciotomy did relieve compartment pressure as intended.

The 3 measures of tissue viability significantly correlated with each other: TVI and HIS ($p=0.016$, Pearson=-0.59), TVI and fibrosis ($p=0.05$, Pearson=-0.494), and HIS and fibrosis ($p=0.01$, Pearson=0.608), i.e., higher TVI correlated with lower HIS and lower fibrosis. The results demonstrate internal consistency among the 3 techniques.

Severity of compartment syndrome as measured by CP significantly correlated with viability measured by TVI ($p=0.029$, Pearson=-0.545), HIS ($p<0.001$, Pearson=0.846), and fibrosis ($p=0.024$, Pearson=0.562). Similarly, significant correlations were observed between ΔP and TVI ($p=0.022$, Pearson=0.567), HIS ($p<0.001$, Pearson=-0.849), and fibrosis ($p=0.014$, Pearson=-0.601).

In contrast to CP and ΔP, no significant correlations were detected between CS PmO2 and viability. No significant correlations were observed between severity of compartment syndrome as measured by PmO2 with any of the viability measurements: TVI ($p=0.43$), HIS ($p=0.385$), fibrosis ($p=0.952$). Similarly, no significant correlations were observed between duration of PmO2<1mmHg or PmO2≤0mmHg and viability: TVI ($p=0.245$ and 0.554, respectively), HIS ($p=0.765$ and 0.559), and fibrosis ($p=0.642$ and 0.955).

Regarding PmO2 following fasciotomy, there was no significant correlation detected between mean postCS PmO2 and any of the viability measurements: TVI ($p=0.271$), HIS ($p=0.484$), and fibrosis ($p=0.676$) nor for the difference between postCS-preCS PmO2 and tissue viability: TVI ($p=0.128$), HIS ($p=0.689$), and fibrosis ($p=0.698$).

In contrast to tourniquet ischemia, recovery to baseline PmO2 did not significantly correlate with any of the viability measurements: TVI (p=0.665), HIS (p=0.885), and fibrosis (p=0.773). Somewhat unexpectedly, a higher postCS PmO2 compared to preCS PmO2 (i.e., post:pre ratio) correlated with lower viability, though this reached statistical significance only for HIS (p=0.02, Pearson=0.596) but not TVI (p=0.1) and fibrosis (p=0.9). A higher post:pre ratio would be consistent with reperfusion that has also been proposed as the pathophysiology of compartment syndrome (see Discussion below). No animal had a mean postCS PmO2 less than 10 mm Hg or less than 50% of mean preCS PmO2, so these comparisons could not be made.

From the tourniquet results we found that greater than 6 hours of tourniquet ischemia, which is the condition expected to cause maximum ischemic necrosis, yielded an average TVI of 0.70. Comparing CS limbs based on this MTT threshold, limbs with higher viability had CS of lower severity as measured by PmO2 and CP, though neither was statistically significant (p=0.153 and 0.064, respectively). Higher viability was also associated with lower post:pre PmO2 ratio, consistent with the results described above, though this was also not statistically significant (p=0.09).

Discussion

Our results lead to the important conclusion that current clinical use of parameters related to direct measurement of compartment pressure (i.e., CP and ΔP) remains justified for the diagnosis of acute extremity compartment syndrome. We made the notable finding that direct measurement of PmO2 does appear to reflect changes associated with compartment syndrome and fasciotomy. Similar degrees of ischemia, as measured by PmO2, could be achieved after tourniquet ischemia and compartment syndrome (specific aim #2): TI PmO2 average was 1.30mmHg for 2:02 to 8:28 hours, during which PmO2<1mmHg ranged from 0 to 494 minutes and ≤0 from 0 to 368 minutes. CS PmO2 average was 3.82mmHg ranging from 0.15 to 10.24mmHg in Phase 1, during which PmO2 <1mmHg ranged from 22.5 to 445 minutes and ≤0 from 5 to 370 minutes. Following release of ischemic conditions, response was an increase in PmO2 for both TI and CS, but only TI had significant correlation with viability.
Despite the strong theoretical benefits and promising preliminary results of observational studies for tissue oxygenation from our group and others, compartment pressure, rather than tissue oxygenation, predicted degree of tissue damage. Our results reinforce the importance of controlled experimentation utilizing well-established models of high translation potential to test novel techniques before advocating implementation for clinical use. The severity of CS induced in our study was similar to previous studies that established widely used thresholds of ΔP in clinical practice[5, 6].

It is generally accepted that compartment syndrome occurs when the pressure inside a fascial compartment increases to such an extent that it limits the circulation's ability to perfuse the area. By this logic a diagnostic technique that allowed us to monitor the ischemia produced by decreased circulation through a direct measure of tissue oxygenation would be a superior method of monitoring and diagnosing ACS than the currently used compartment pressure, which is an indirect measure of presumed tissue ischemia. PmO2 should, in theory, correlate well with compartment pressures because as the compartment pressures rise the circulation should decrease and be reflected by lower PmO2. Because the technique studied allows direct

measurement of tissue oxygen, we had hypothesized that clear thresholds of duration and severity for irreversible necrosis could be identified, but the results reject this hypothesis.

Previous studies have demonstrated the safety and feasibility of using direct measurement of tissue oxygenation in various clinical settings and furthermore suggested that it may demonstrate a lower false positive rate than traditional compartment pressure monitoring[7]. It is important to note that these were observational and uncontrolled. A similar but distinct approach also based on tissue oxygenation is near-infrared spectroscopy (NIRS), which monitors the percentage of hemoglobin saturation[8 9-13]. Studies utilizing NIRS to monitor tissue perfusion in animal models reported that hemoglobin saturation correlated with compartment pressure measurements seen in compartment syndrome as well as neurologic dysfunction (loss of twitch reflex)[12]. However, these studies, unlike ours and the highly cited historical studies, did not utilize the dog model and did not include survival post-experimentally that is necessary to assess tissue viability. It should be noted that our study also found that PmO2 was responsive to ischemic conditions; PmO2 significantly decreased after induction of compartment syndrome and recovered after fasciotomy. These initial observations did not ultimately correlate with tissue viability 2 weeks later. Considering that the technique studies in our study is a direct measurement of tissue oxygenation, which NIRS attempts to measure indirectly and non-invasively, it is unlikely that this approach is a viable method of diagnosis.

After tourniquet ischemia, final PmO2 did appear to predict tissue viability. That no other significant associations were detected is not surprising. The results suggest that as long as postTI PmO2 is at least equal to baseline preTI PmO2, tissue viability will remain similar despite fluctuations. Wide variability was also noted in the preTI PmO2 value, so this resulted in a floor effect because PmO2 decreased to 0 in all cases; a low starting preTI PmO2 would therefore result in being considered lower severity than a high starting preTI PmO2, even though the tourniquet time and tourniquet PmO2 are similar, because severity in terms of PmO2 was measured as the difference from baseline.

Different results were obtained for compartment syndrome. Final postCS PmO2 did not predict tissue viability, nor did any of the other variables utilizing PmO2. In contrast, variables based on compartment pressure (CP and ΔP) did correlate significantly with all measures of tissue viability. Therefore, warning criterion based on PmO2 by comparing tissue oxygenation and pressure in compartment syndrome of known severities (specific aim #1) was not found. Because CS PmO2 did not significantly correlate with the CP or ΔP, we could not determine PmO2 values associated with certain values of CP (e.g., $\Delta P<20$mmHg). Since postCS PmO2 did not correlate with viability, a PmO2 threshold for irreversible necrosis was not found (specific aim #3). Utilizing a threshold of TVI 0.7 (viability after greater than 6 hours of warm ischemia), no value of PmO2 could be significantly associated with this degree of necrosis.

This may be because the pathophysiology of compartment syndrome is likely more complex than simple ischemia. Heppenstall, et al compared compartment syndrome and tourniquet ischemia of equal duration in 10 dogs[14]. They measured phosphocreatine, ATP, and intra-cellular pH over time using 31phosphorous nuclear magnetic-resonance spectroscopy. Initially, patterns of phosphocreatine degradation after induction of tourniquet ischemia and compartment syndrome were similar and consistent with a condition of complete ischemia. However, recovery was different after tourniquet release or fasciotomy. The tourniquet group

recovered completely within minutes; the compartment syndrome group showed sluggish recovery that was incomplete after 2 hours. Compared to the tourniquet group, the compartment syndrome group showed was rapid and severe depletion of cellular ATP, lower pH, and greater cellular damage on electron microscopy. The authors concluded that compartment syndrome produced a synergy of ischemia and pressure to cause more severe degree of cell damage.

Compartment pressure may be representative of not only ischemia but overall tissue damage and therefore the superior method of diagnosis, as our results suggest. Hargens, et al. induced compartment syndrome of high severity (up to 120mmHg for 8 hours) in 28 dogs and measured uptake of technetium-99m stannous pyrophosphate by scintigraphy 48 later, which they stated is specific to irreversible ischemic injury[15]. Uptake increased exponentially based on pressure with a reported correlation coefficient of 0.987 with apparent ceiling. This was consistent with qualitative analysis of H&E based on used cellular infiltration and degeneration of fiber structure, floccular changes, hyaline degeneration, vacuolization, fiber-splitting, displacement of sarcolemmal nuclei, and changes in fiber size. Unlike PmO2, which demonstrated a floor effect in our study, CP has no ceiling, and more severe CP and ΔP correlated significantly with worse viability.

The tissue oxygenation technique utilized in our study also does not account for another potential mechanism of injury: reperfusion. Our results suggest, though this did not reach statistical significance, that a higher ratio of postCS PmO2 compared to preCS PmO2 correlated with lower viability, which would be consistent with reperfusion injury. Seekamp, et al. performed a compartment syndrome study in rats by measuring PmO2 in the lower extremities after temporary intrabdominal ligature of the aorta[16]. Restoring blood flow after 4 hours of ligature resulted in elevated CP and low PmO2. Adding prophylactic fasciotomy prevented CP and showed recovery of PmO2. After 6 hours, a no reflow situation occurred in which there was no compartment syndrome but also no increase in PmO2.

In addition to the above discussion regarding a more complex mechanism of injury than simple ischemia, a further limitation of direct measurement of tissue oxygenation is a floor effect. Very low values of PmO2 including <1 and ≤ 0 were measured for prolonged durations but were not associated with lower viability. With CP and ΔP, there is no ceiling; higher pressure can always be measured. However, when PmO2 measurements cannot fall below 0, and therefore the severity of CS may not be comparable based on PmO2 alone.

An additional barrier to identification of threshold values for reversible or irreversible necrosis was the unexpectedly narrow range of TVI. In Phase 1, these ranged from 64.84% to 105.84%, but the standard deviation, at14.6%, was relatively large making it difficult to distinguish high from low degrees of necrosis. Despite this shortcoming, it is notable that TVI, HIS, and fibrosis showed statistically significant consistency.

Phase 1 included 16 animals, not 20 as initially proposed, because of higher animal expenses as expected, but this is not thought to have affected the study conclusions. Electron microscopy was also not utilized, but it is unlikely that this qualitative assessment would have added meaningfully to the analysis of tissue viability. It was difficult to maintain CP conditions separated by 10mmgHg as initially proposed. However, any difference in time or duration was accounted for by the statistical analysis.

b) Phase 2 significant results and key outcomes

There was a significant difference between preCS PmO2 and CS PmO2 (45.63→6.17 mmHg, p<=0.001); no fasciotomy was performed. Tissue oxygenation measurements reflected the underlying changes in tissue oxygenation as compartment syndrome was induced. In Phase 2 the average CS PmO2 was 6.17mmHg (range 0.11 to 20.10), during which and PmO2<1 for 0-432.5 minutes and ≤0mmHg for 0-409.5 minutes. CS PmO2 did not correlate significantly with CP or ΔP.

Per the proposal, in Phase 2 compartment syndrome severity was based on PmO2. No statistically significant correlations were detected between viability and all of the PmO2 and CP parameters (see Phase 1 statistical analysis above). Severity of the compartment syndromes as measured by PmO2 was more severe than Phase 1. However, severity of the compartment syndromes as measured by CP and ΔP was milder than Phase 1. Due to floor effect of PmO2 described above, CS of very low PmO2 would have to be induced in order to produce low TVI. Even with 218.5 minutes average of Pm<1mmHg (ranging up to 432.5 minutes), no differences among TVI could be discerned. Most importantly, because CP and ΔP were found in Phase 1 to be significant predictors of viability, it is likely that compartment syndromes induced in Phase 2 were not severe enough to create distinguishable differences in tissue viability. Therefore, compartment syndrome based on tissue oxygenation (specific aim #4) did not result in predictable degrees of necrosis.

Phase 2 included 8 animals, not 10 as initially proposed, because it was apparent that PmO2 was not a useful variable on which to base severity of compartment syndrome. Electron microscopy was also not utilized, but it is unlikely that this qualitative assessment would have added meaningfully to the analysis of tissue viability. It was difficult to maintain CP conditions separated by 10mmgHg as initially proposed. However, any difference in time or duration was accounted for by the statistical analysis.

c) Phase 3 significant results and key outcomes

In Phase 3 we investigated the effectiveness of nonsurgical treatments for compartment syndrome compared to fasciotomy (specific aim #5). First, we examined the effect of fasciotomy in 8 animals with CS treated with pressors. One limb (n=6) had fasciotomy and the rest of the limbs did not (n=10). After fasciotomy, PmO2 increased from 18.22 to 28.26 (p=0.5 by Wilcoxan ranked sums test for paired non-parametric data); 4 out of 6 limbs increased <5mmHg. This is in marked contrast to Phase 1 where PmO2 increase after fasciotomy averaged 46.37mmHg (range 12.52 to 81.31) after fasciotomy. This difference did not reach statistical significance (p=0.07). Although the limbs that did not undergo fasciotomy had higher severity as measured by CP (p=0.004) and ΔP (p=0.36), there was no significant differences in TVI and HIS, and fibrosis was found to be significantly higher in the fasciotomy group (p=0.038). The results suggest that fasciotomy had no additional effect on TVI if the limb was treated with pressors.

Second, we compared to Phase 2, in which no pressors were used. We found a significant difference in the degree of ischemia after induction of compartment syndrome. There was no significant difference between preCS PmO2 (Phase 2= 45.63mmHg, Phase 3=34.66mmHg), but induction of compartment syndrome led to larger decrease in PmO2 in the

Phase 2 legs (-39.46 vs. -20.75mmHg, p=0.008). This is despite the fact that CS as measured by CP was more severe in Phase 3 (Phase 3=99.69mmHg, Phase 2=54.85, p<0.001). The use of pressors mitigated the decrease in PmO2 normally observed after induction of CS.

We then studied the effect of pressors on tissue viability by comparing limbs that underwent CS without fasciotomy that did or did not receive pressors (i.e., Phase 2 limbs and Phase 3 limbs treated with pressors). To account for the difference in CS severity between Phase 2 and Phase 3, a linear regression was performed to control for the variable severity of CS. The dependent variable was TVI. The independent variables were use of pressors (yes/no) and severity of CS as measured by ΔP*time. (Phase 1 experiments revealed that ΔP*time was the greatest predictor of viability as measured by TVI.) For the CS induced in Phase 2 and 3, the model was valid (R2=0.284, p=0.02) and revealed use of pressors as a statistically significant independent predictor of MTT (unstandardized coefficient 0.377, p=0.05) where ΔP*time was not significant (p=0.9).

The phase 3 results indicate that use of pressors was a significant predictor of higher TVI. It also showed no added benefit with fasciotomy in the animals treated with pressors, even though the conditions were more severe. The higher fibrosis may be from the damage of the fasciotomy itself. The results suggest that medical management in the form of vasoactive and inotropic drugs may mitigate compartment syndrome.

There have been few studies investigating a possible non-surgical approach to compartment syndrome. To our knowledge, the only drug previously tested to treat compartment syndrome is mannitol. Mannitol has shown promising results in a previous dog study, diminishing compartment syndrome due to its osmotic activity, decreasing the amount of interstitial fluid in the affected compartment[17]. The usefulness in humans with compartment syndrome was examined in one case report and shown to be moderately effective[18]. However, several case reports have shown that intravenous extravasation of mannitol can induce compartment syndrome [19-21]. These and other risks associated with intravenous mannitol therapy have likely discouraged further pursuit of it as a potential treatment for compartment syndrome.

Hypotension has been shown to decrease perfusion to the affected compartment and worsen tissue injury [22]. It follows that a therapy that increases perfusion pressure to the extremity could decrease the ischemic damage to the tissue. Therefore, selecting an agent that maintains blood pressure in potential settings of hypotension along with an agent that can increase cardiac output should create an environment in which blood flow is increased to a high-pressure compartment. Additionally, leakage of plasma from intravascular space into tissue compartments has been linked to compartment syndrome [23]. It is therefore rational that a therapy that prevents loss of fluid through the vessels, such as a vasoconstrictor, could slow down or even reduce the increasing compartment pressure. For these reasons, we selected the vasoconstrictor phenylephrine and the inotropic agent dobutamine.

Phenylephrine is a potent, selective α1-adrenergic receptor agonist used in the operating room and ICU to maintain arterial pressure. It increases blood pressure purely via vasoconstriction with no direct effect on heart rate or contractility. The ability to maintain arterial pressure makes it a truly valuable agent in situations in which hypotension and the potential for ischemic injury is a concern. Hypotension after induction of anesthesia occurs commonly in both humans and animals, including dogs [24, 25]. Vasoconstrictors, such as

phenylephrine, can play a valuable role in maintaining proper blood pressure and preventing ischemic injury in an anesthetized patient. Because of its rapid onset and purely vasoactive effects, phenylephrine is an appealing agent in hypotensive septic patients [26]. Phenylephrine is also commonly used to treat hypotension during obstetric procedures and maintain blood pressure in traumatic brain injuries [27, 28]. However, in high doses, phenylephrine has the potential for a reflexive baroreceptor-mediated decrease in cardiac output. Because of this, dobutamine was added in our model. Dobutamine is an inotropic agent commonly used in patients with cardiogenic shock to increase heart rate, contractility, and cardiac output. This agent has been shown to increase blood flow to the limbs in patients with congestive heart failure during exercise [29, 30]. The use of dobutamine and phenylephrine together was examined in one retrospective analysis of patients with septic shock[31]. This combination resulted in an increased MAP without a compromise in heart rate.

It should be noted that vasoactive drugs such as phenylephrine and inotropic drugs such as dobutamine do have serious risks associated with their use. Excessive vasoconstriction or reflex bradycardia with the use of α1-adrenergic receptor agonists can lead to inadequate perfusion to end-organs and extremities. Therefore, careful monitoring of hemodynamic status and coupling with inotropic agents are important with their use. This is particularly important when applied to their potential use in compartment syndrome, in which the patients cannot afford a further drop in perfusion. Certain vasopressors and inotropic drugs carry the risk of causing dysrhythmias including sinus tachycardia, atrial fibrillation, and ventricular tachyarrhythmias.

There have been case reports of vasopressors exacerbating compartment syndrome. One report involved the development of compartment syndrome in uninjured limbs. In this hypotensive trauma patient, high dose, systemic epinephrine was given after resuscitation efforts [32]. Compartment syndrome developed in several extremities in the days following requiring fasciotomy. Another case report discussed the development of bilateral anterior tibial compartment syndrome after ingestion of high dose ergotamine for a migraine[33]. This patient also required fasciotomy. These case reports show that vasoactive drugs need to be careful administered and monitored to avoid potentially devastating adverse events. However, our results show that these agents may also have potential to be useful in patients with compartment syndrome when used carefully with inotropic drugs. This highlights that these drugs merit further study of their potential therapeutic or deleterious impact on patients with or at risk for extremity compartment syndrome.

Considerable experience was gained with the implantation and use of the tissue oxygen probe, but despite this familiarity, it remained a technically challenging exercise that makes practical use in its current form unlikely. An additional problem with the probe was that left-to-right differences of PmO2 occurred within the same animal at baseline before any experimental procedures were performed. These differences averaged 19.88mmHg (range 3.99 to 50.56mmHg). They suggest that there may be variability in the distribution of PmO2 within the same muscle compartment, which would greatly impair the feasibility of this technique because of the risk of sampling error. It may also explain the lack of significant correlations between PmO2 and TVI in many parts of the study.

CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

Changes were minor and not felt to impact the results of the study:

- The number of animals was reduced from 40 to 32 (Phase 1 n=16, Phase 2 n=8, Phase 3 n=8) because of higher animal expenses incurred than budgeted during transfer of the study to a different facility (see below). It is not felt that the lower number of animals affected the findings of the study.
- Hydroxyethyl starch (Hespan) was used for infusion because of more convenient storage at room temperature, accessibility, and equivalent osmolality as the originally planned colloid solution.
- The thigh muscle (quadriceps) was used as control, rather than forelimb, because of easy access to the thigh and difficult access to the forelimb, which was smaller.

▪ **Actual or anticipated problems or delays and actions or plans to resolve them**

The study beginning was delayed because the facility described in the proposal, the Laboratory Animal Research Center at the University of California, San Francisco, signaled their unwillingness to perform survival experiments in dogs and would only accommodate non-survival experiments in this animal model. The Institutional Animal Care and Use Committee of the San Francisco Veterans Affairs refused to approve the protocol because of the use of a dog model. Therefore, an alternative animal care facility had to be identified and a new budget drafted.

▪ **Changes that had a significant impact on expenditures**

Nothing to report

▪ **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

4. KEY RESEARCH ACCOMPLISHMENTS

We have developed a reliable and reproducible technique for implantation and use of this tissue oxygen probe for continuous direct monitoring of intramuscular tissue oxygenation for further basic science or clinical research in orthopedic trauma, including extremity compartment syndrome.

5. CONCLUSION:

▪ **What was the impact on the development of the principal discipline(s) of the project?**

The impact on orthopaedic trauma surgeon and military surgeons treating extremity trauma is to reinforce the current approach to this problem. Acute extremity compartment syndrome is a clinical diagnosis that cannot be made based on objective criteria alone. Current diagnostic techniques that utilize direct measurement of compartment pressure are valid. However, as is current practice, clinicians should maintain a high level of suspicion. Emphasis should remain early intervention with fasciotomy, even if the diagnosis is uncertain, and it should continue to be considered a surgical emergency. Tissue oxygenation for diagnosis of compartment syndrome is an active area of research within the field. The results of our large and comprehensive study, whose strengths include experimental techniques from widely accepted historical studies combined with quantitative assessment of tissue viability, indicate that tissue oxygenation may not be a feasible approach to this problem.

- **What was the impact on other disciplines?**

The results of Phase 3 of this study may impact other disciplines that prescribe vasoactive agents. In the setting of compartment syndrome, if clinically appropriate, use of phenylephrine and/or dobutamine may decrease the risk of acute extremity compartment syndrome. These disciplines include anesthesia and critical care medicine, emergency medicine, and internal medicine.

- **What was the impact on technology transfer?**

Nothing to report. The results of our study reinforce current thinking of compartment syndrome as a clinical diagnosis that requires aggressive intervention even if the diagnosis is uncertain. It decreases the feasibility of strategies that utilize technologies related to tissue oxygenation to achieve a novel method of diagnosis of acute extremity compartment syndrome that is accurate, real-time, and can guide treatment.

- **What was the impact on society beyond science and technology?**

The general public understands that extremity trauma is a major cause of morbidity in combat casualties. The study results show that one common type of injury, acute extremity compartment syndrome, is a difficult problem that cannot be addressed simply by technology for diagnosis and treatment. It highlights the need for a robust combat health support system that is readily accessible by the medical evaluation chain and staffed by skilled surgeons who can assess, recognize, and treat compartment syndrome. The study contributes to the understanding by society that conditions like compartment syndrome necessitate an adequate medical infrastructure to support military operations.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

A) Publications:

- **Lay Press:**
  Nothing to report

- **Peer-Reviewed Scientific Journals:**
  1. Hansen EN, Manzano G, Kandemir U, Mok JM: Comparison of tissue oxygenation and compartment pressure following tibia fracture. Injury 2013 Aug;44(8):1076-80. doi: 10.1016/j.injury.2012.11.012. Epub 2012 Dec 21. PMID: 23265784

- **Invited Articles:**
  1. Mok JM, Hansen EN, Kim H, Kandemir U: Diagnosis of Acute Compartment Syndrome: Direct Measurement of Tissue Oxygenation. Techniques in Orthopaedics 2012 Mar;27(1):22-29.

- **Abstracts:**

  1. Mok JM, Hansen EN, Kandemir U: Measurement of Intramuscular Tissue Oxygenation During Compartment Syndrome in a Dog Model. Podium Presentation. Society of Military Orthopaedic Surgeons 53rd Annual Meeting, San Diego, California, December 12-16, 2011.
  2. Kang H, Mok J, Hansen E, Kandemir U, Rollins M, Manzano G, Liu X, Kim H: A Canine Model for Measuring Tissue Oxygenation as a Diagnosis of Compartment Syndrome. Poster Presentation. 58th Orthopaedic Research Society Annual Meeting, San Francisco, California, February 4-7, 2012.

3. Mok JM, Hansen EN, Kandemir U: Measurement of Intramuscular Tissue Oxygenation During Compartment Syndrome in a Dog Model. Podium Presentation. American Academy of Orthopaedic Surgeons Annual Meeting, San Francisco, California, February 7-11, 2012.
4. Mok J, Kang H, Hansen E, Kandemir U, Rollins M, Kim H: Relationship Of Intramuscular Tissue Oxygenation And Muscle Viability In A Compartment Syndrome Model. Poster Presentation. 29th Annual Meeting of the Orthopaedic Trauma Association, Phoenix, Arizona, October 9-12, 2013.
5. Liu X, Mok J, Kang H, Jin J, Boehme A, Hansen E, Kandemir U, Rollins M, Kim HT: Non-operative Treatment For Compartment Syndrome With Phenylephrine and Dobutamine. Poster Presentation. 60th Annual Meeting of the Orthopaedic Research Society, New Orleans, Louisiana, March 15-18, 2014.
6. Mok JM, Hansen EN, Rollins M, Liu X, Kandemir U: Intramuscular Tissue Oxygenation Correlates with Muscle Viability in Treated and Untreated Compartment Syndrome. Podium Presentation. 2014 American Orthopaedic Association/Canadian Orthopaedic Association Combined Meeting, Montreal, Quebec, June 18-21, 2014.

B) Presentations made during the last year

1. **Poster Presentation** Liu X, Mok J, Kang H, Jin J, Boehme A, Hansen E, Kandemir U, Rollins M, Kim HT: Non-operative Treatment For Compartment Syndrome With Phenylephrine and Dobutamine. Poster Presentation. 60th Annual Meeting of the Orthopaedic Research Society, New Orleans, Louisiana, March 15-18, 2014.
2. **Poster Presentation** Mok JM, Hansen EN, Rollins M, Liu X, Kandemir U: Intramuscular Tissue Oxygenation Correlates with Muscle Viability in Treated and Untreated Compartment Syndrome. Podium Presentation. 2014 American Orthopaedic Association/Canadian Orthopaedic Association Combined Meeting, Montreal, Quebec, June 18-21, 2014.

7. Inventions, Patents and Licenses

Nothing to report.

8. REPORTABLE OUTCOMES:

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We introduced and validated a technique for assessment of muscle viability that represents an adaption of the method of Crawford, et al. The Tissue Viability Index was modified by controlling for between-animal differences by normalizing to a muscle specimen from the quadriceps (unaffected by experiments). We validated it by showing statistically significant correlations with HIS and fibrosis. To our knowledge, this technique has not been applied to skeletal muscle in an infusion model of compartment syndrome. As a quantitative measure of necrosis, this represents an important contribution to the methodology of future studies on compartment syndrome.

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9. OTHER ACHIEVEMENTS:

Nothing to report

10. REFERENCES

1. Crawford RS, Hashmi FF, Jones JE, Albadawi H, McCormack M, Eberlin K, Entabi F, Atkins MD, Conrad MF, Austen WG, Jr., Watkins MT: A novel model of acute murine hindlimb ischemia, Am J Physiol Heart Circ Physiol 2007, 292:H830-837
2. McCormack MC, Kwon E, Eberlin KR, Randolph M, Friend DS, Thomas AC, Watkins MT, Austen WG, Jr.: Development of reproducible histologic injury severity scores: skeletal muscle reperfusion injury, Surgery 2008, 143:126-133
3. Tanaka M, Fujiwara H, Onodera T, Wu DJ, Hamashima Y, Kawai C: Quantitative analysis of myocardial fibrosis in normals, hypertensive hearts, and hypertrophic cardiomyopathy, Br Heart J 1986, 55:575-581
4. Sato K, Li Y, Foster W, Fukushima K, Badlani N, Adachi N, Usas A, Fu FH, Huard J: Improvement of muscle healing through enhancement of muscle regeneration and prevention of fibrosis, Muscle Nerve 2003, 28:365-372
5. Heckman MM, Whitesides TE, Jr., Grewe SR, Judd RL, Miller M, Lawrence JH, 3rd: Histologic determination of the ischemic threshold of muscle in the canine compartment syndrome model, J Orthop Trauma 1993, 7:199-210
6. Matava MJ, Whitesides TE, Jr., Seiler JG, 3rd, Hewan-Lowe K, Hutton WC: Determination of the compartment pressure threshold of muscle ischemia in a canine model, J Trauma 1994, 37:50-58
7. Hansen EN, Manzano G, Kandemir U, Mok JM: Comparison of tissue oxygenation and compartment pressure following tibia fracture, Injury 2013, 44:1076-1080
8. Cathcart CC, Shuler MS, Freedman BA, Reno LR, Budsberg SC: Correlation of near-infrared spectroscopy and direct pressure monitoring in an acute porcine compartmental syndrome model, J Orthop Trauma 2014, 28:365-369
9. Shuler MS, Reisman WM, Kinsey TL, Whitesides TE, Jr., Hammerberg EM, Davila MG, Moore TJ: Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg, J Bone Joint Surg Am 2010, 92:863-870
10. Shuler MS, Reisman WM, Whitesides TE, Jr., Kinsey TL, Hammerberg EM, Davila MG, Moore TJ: Near-infrared spectroscopy in lower extremity trauma, J Bone Joint Surg Am 2009, 91:1360-1368
11. Mancini DM, Bolinger L, Li H, Kendrick K, Chance B, Wilson JR: Validation of near-infrared spectroscopy in humans, J Appl Physiol (1985) 1994, 77:2740-2747
12. Garr JL, Gentilello LM, Cole PA, Mock CN, Matsen FA, 3rd: Monitoring for compartmental syndrome using near-infrared spectroscopy: a noninvasive, continuous, transcutaneous monitoring technique, J Trauma 1999, 46:613-616; discussion 617-618
13. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, Cleland A, Schaefer B, Irwin B, Fox S: Monitoring brain oxygen saturation during coronary bypass surgery: a randomized, prospective study, Anesth Analg 2007, 104:51-58
14. Heppenstall RB, Scott R, Sapega A, Park YS, Chance B: A comparative study of the tolerance of skeletal muscle to ischemia. Tourniquet application compared with acute compartment syndrome, J Bone Joint Surg Am 1986, 68:820-828
15. Hargens AR, Schmidt DA, Evans KL, Gonsalves MR, Cologne JB, Garfin SR, Mubarak SJ, Hagan PL, Akeson WH: Quantitation of skeletal-muscle necrosis in a model compartment syndrome, J Bone Joint Surg Am 1981, 63:631-636

16. Seekamp A, Van Griensven M, Blankenburg H, Regel G: Intramuscular partial oxygen tension monitoring in compartment syndrome--an experimental study, Eur J Emerg Med 1997, 4:185-192
17. Better OS, Zinman C, Reis DN, Har-Shai Y, Rubinstein I, Abassi Z: Hypertonic mannitol ameliorates intracompartmental tamponade in model compartment syndrome in the dog, Nephron 1991, 58:344-346
18. Daniels M, Reichman J, Brezis M: Mannitol treatment for acute compartment syndrome, Nephron 1998, 79:492-493
19. Erickson BA, Yap RL, Pazona JF, Hartigan BJ, Smith ND: Mannitol extravasation during partial nephrectomy leading to forearm compartment syndrome, Int Braz J Urol 2007, 33:68-71; discussion 71
20. Eroglu A, Uzunlar H: Forearm compartment syndrome after intravenous mannitol extravasation in a carbosulfan poisoning patient, J Toxicol Clin Toxicol 2004, 42:649-652
21. Edwards JJ, Samuels D, Fu ES: Forearm compartment syndrome from intravenous mannitol extravasation during general anesthesia, Anesth Analg 2003, 96:245-246, table of contents
22. Donaldson J, Haddad B, Khan WS: The pathophysiology, diagnosis and current management of acute compartment syndrome, Open Orthop J 2014, 8:185-193
23. Lamou H, Grassmann JP, Betsch M, Wild M, Hakimi M, Windolf J, Jungbluth P: Systemic capillary leak syndrome associated with a rare abdominal and four-limb compartment syndrome: a case report, J Med Case Rep 2014, 8:196
24. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, Bodian CA: Predictors of hypotension after induction of general anesthesia, Anesth Analg 2005, 101:622-628, table of contents
25. Iizuka T, Kamata M, Yanagawa M, Nishimura R: Incidence of intraoperative hypotension during isoflurane-fentanyl and propofol-fentanyl anaesthesia in dogs, Vet J 2013, 198:289-291
26. Hollenberg SM: Inotrope and vasopressor therapy of septic shock, Crit Care Nurs Clin North Am 2011, 23:127-148
27. Heesen M, Kolhr S, Rossaint R, Straube S: Prophylactic phenylephrine for caesarean section under spinal anaesthesia: systematic review and meta-analysis, Anaesthesia 2014, 69:143-165
28. Sookplung P, Siriussawakul A, Malakouti A, Sharma D, Wang J, Souter MJ, Chesnut RM, Vavilala MS: Vasopressor use and effect on blood pressure after severe adult traumatic brain injury, Neurocrit Care 2011, 15:46-54
29. Delehanty J, Liang CS, Odorisi ML: Effects of dobutamine on ischemic vasodilation of the forearm in patients with severe congestive heart failure, J Card Fail 1999, 5:25-30
30. Mancini DM, Schwartz M, Ferraro N, Seestedt R, Chance B, Wilson JR: Effect of dobutamine on skeletal muscle metabolism in patients with congestive heart failure, Am J Cardiol 1990, 65:1121-1126
31. Gregory JS, Bonfiglio MF, Dasta JF, Reilley TE, Townsend MC, Flancbaum L: Experience with phenylephrine as a component of the pharmacologic support of septic shock, Crit Care Med 1991, 19:1395-1400
32. Hoang C, Porter JM, Ursic CM: Compartment syndrome in multiple uninjured extremities: a case report, Am Surg 2002, 68:127-129

33. Elliott MJ, Glass KD: Anterior tibial compartment syndrome associated with ergotamine ingestion, Clin Orthop Relat Res 1976, 44-46

11. APPENDICES:

A) 2011 OMOS abstract

INTRODUCTION

Acute compartment syndrome is a potentially devastating complication of extremity trauma with dismal outcomes reported after late treatment. It remains a problematic area due to difficulty of timely and accurate diagnosis. Direct measurement of tissue oxygenation may represent a novel method of diagnosis that is continuous, physiologic, and specific. We have previously shown that measurement of tissue oxygenation (PmO2) with a percutaneously placed intramuscular probe was feasible and highly sensitive to tourniquet-induced ischemia. In this prospective observational study, continuous simultaneous monitoring of tissue oxygenation and compartment pressure (CP) was performed in patients following intramedullary nailing of tibia fracture. The number of measurements meeting pre-defined warning criteria for tissue oxygenation and compartment pressure was compared.

METHODS

Patients meeting inclusion criteria (minimum 18 years of age, Emergency Department admission, unilateral isolated closed acute tibial shaft fracture, planned treatment with intramedullary nailing, ability to give informed consent) were asked to enroll in the study. All participants gave their informed consent. With the patient under anesthesia, a polarographic tissue oxygenation probe and a compartment pressure probe were placed percutaneously under sterile conditions into the anterior compartment of the leg using a Seldinger technique. PmO2 and CP were recorded continuously for 48 hours post-operatively or until the patient mobilized with the physical therapist. The patient and all care providers were blinded to the measurements. Two warning criteria were used for CP based on the literature: absolute CP>30mm Hg and perfusion pressure (ΔP = diastolic blood pressure-CP)<30mm Hg. Warning criterion for tissue oxygenation was PmO2<10mmHg, which has been suggested for monitoring of free flaps.

RESULTS

12 patients were enrolled. One patient underwent intra-operative fasciotomy and was excluded. Therefore, the experimental arm consisted of 11 patients. No clinically apparent compartment syndrome occurred post-operatively. No complications occurred, and probes were well tolerated. Mean duration of CP measurements was 33.4 hours. All patients eligible for comparison of PmO2 vs. absolute CP displayed measurements meeting warning criterion of CP>30mmHg in the absence of compartment syndrome, with a mean of 46.2% (range, 3.81-99.9) of measurements. In contrast, concurrent PmO2 measurements meeting warning criteria of PmO2<10mmHg occurred in 2 patients (0.58%, 6.91%) for a mean of 0.75%. The difference in the proportions meeting warning criteria was statistically significant. Eight of 9 patients eligible for comparison of PmO2 vs. perfusion pressure had measurements meeting warning criterion of ΔP<30mmHg in the absence of compartment syndrome, with a mean of 31% (range, 0-97.7) of

measurements. Concurrent PmO2 measurements meeting warning criteria of PmO2<10mmHg occurred in 1 patient (6.83%) for a mean of 0.76%.

DISCUSSION

In the postoperative period following tibia fracture surgery, continuous monitoring of tissue oxygenation was possible for a prolonged duration and appeared to show higher specificity than compartment pressure, i.e., a very small portion of PmO2 measurements met warning criterion in the absence of compartment syndrome, compared to 46.2% of CP and 31% of ΔP. This is consistent with previous reports noting the poor specificity of intracompartmental pressure and that reliance on this modality may lead to excessive fasciotomy. Although no compartment syndrome occurred and therefore no comparison could be made, it is noteworthy that a pre-defined PmO2 threshold of 10mmHg did appear to demonstrate a high level of specificity (i.e., low false positive rate) compared to CP, which is the main objective test currently in use.

B) 2012 AAOS Abstract

Introduction:
Acute compartment syndrome (CS) remains a problematic area due to difficulty of diagnosis. Continuous measurement of intramuscular tissue oxygenation (PmO2) of the leg has been shown to be feasible in humans and highly sensitive to tourniquet-induced ischemia (TI). We investigated the effect of induced compartment syndrome on PmO2 under controlled conditions in a dog model.

Methods:
This pilot non-survival animal study included 6 female beagles. Animals remained under general anesthesia. Polarographic oxygen probes were placed percutaneously into the anterolateral compartment muscle of the legs bilaterally. PmO2 was recorded every 30 seconds. In the control limb, tourniquet was placed on the thigh and inflated to 200mmHg. In the CS limb, Hespan was infused through an intramuscular angiocath to induce and maintain a compartment pressure 30mmHg above the diastolic blood pressure as measured by arterial line. After approximately 6 hours of compartment syndrome, fasciotomy was performed. Animals were euthanized at the conclusion of experiments.

Results:
Mean duration of compartment syndrome was 5.9 hours. The averaged mean PmO2 of the CS limb was 30.71mmHg (range, 10.56-50.18) before infusion and decreased in all animals to 1.34mmHg (-0.06-3.65) during induced CS ($p<0.05$ by Wilcoxan ranked sums test). Immediately before fasciotomy, the averaged mean PmO2 was -0.20 (-0.50-0.41). Following fasciotomy, PmO2 rapidly increased in all animals to an averaged mean of 38.89 (2.41-90.40, $p<0.05$). In the control limb, PmO2 decreased to 0mmHg in all animals with use of the tourniquet.

Conclusion:
We demonstrated that a severe compartment syndrome using an infusion method results in substantial decrease in PmO2 to values similar to tourniquet-induced ischemia. PmO2 was responsive to changes in tissue oxygenation, as shown by the increase of PmO2 after fasciotomy. Therefore, measurement of intramuscular tissue oxygenation appears to detect pressure-induced ischemia in an animal model with high translational potential. It may represent a minimally invasive, physiologic, and continuous method for diagnosing compartment syndrome.

C) 2014 AOA abstract

Intramuscular Tissue Oxygenation Correlates with Muscle Viability in Treated and Untreated Compartment Syndrome

James Mok, Heejae Kang, Erik Hansen, Xuhui Lu, Utku Kandemir

INTRODUCTION:

The diagnosis of acute compartment syndrome (CS) remains problematic due to difficulty in diagnosis. Continuous measurement of intramuscular tissue oxygenation (PmO2) of the leg has been shown to be feasible in humans and highly responsive to induced compartment syndrome and fasciotomy in a dog model. Using the same animal model, we investigate the relationship between PmO2 measurements and quantitative biochemical tests of tissue viability. Two experimental conditions were studied. The first was CS that was induced to a specified PmO2 and left untreated. The second was ischemia due to induced CS or tourniquet ischemia (TI) that was treated with fasciotomy or release of tourniquet.

METHODS:

The first experiment included 8 legs in 4 animals. Under general anesthesia, CS was induced in the anterolateral compartment via Hespan infusion titrated to a goal PmO2 of 0, 2-4, or 5-10mmHg and maintained for approximately 7 hours. The second experiment included 32 legs in 16 animals. In one leg, CS was induced to a goal compartment pressure of 0, 10, or 30mmHg above diastolic blood pressure, followed by fasciotomy after approximately 7 hours. In the contralateral leg, TI of 2, 4, 6, or 8 hours was induced. In both experiments, after 2 weeks, animals were euthanized at which point muscle biopsies were performed. Tissue viability was assessed by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, a validated technique in which viability is expressed as a percentage of control.

RESULTS:

Mean duration of compartment syndrome in all legs was 7.1 hours. In the first experiment, the averaged mean PmO2 decreased from 47.5mmHg (20-73.2) to 5.7mmHg (0.02-17.5) during induced CS ($p=0.01$). After 2 weeks, mean MTT was 75.5% (60.1-98.6). MTT significantly correlated with the PmO2 of induced CS, with lower PmO2 resulting in lower MTT ($R2=0.53$, $p<0.05$). In the second experiment, the averaged mean PmO2 decreased from 34.4mmHg (15.2-53.7) to 3.08mmHg (0.09-10.3) during induced CS ($p=0.001$) and from 36.3 (24.7-71.8) to 0.7 (0-5.4) during TI ($p<0.001$). MTT significantly correlated with duration and severity of CS ($R2=0.29$, $p<0.05$) and TI ($R2=0.27$, $p<0.05$). Among both CS and TI legs, final PmO2 was less than 10mmHg in 2 animals and less than 50% of pre-CS PmO2 in 4. Viability was significantly lower when final PmO2 was less than 10mmHg (38% vs. 72%, $p=0.02$) or less than 50% of initial PmO2 (52% vs. 73%, $p=0.01$).

CONCLUSIONS:

These results indicate that values of PmO2 during CS reflect the degree of muscle involvement using a quantitative assessment of viability. In addition, final PmO2 values following treatment of CS or TI appear to reflect underlying muscle viability with use of previously suggested threshold criteria (<10mmHg or <50% initial PmO2). Measurement of intramuscular tissue oxygenation detects pressure-induced ischemia and, importantly, appears to correlate with degree of necrosis in an animal model with high translational potential. It may represent a minimally invasive, physiologic, and continuous method to aid in the diagnosis and timing of treatment of compartment syndrome.

D) 2012 ORS abstract

E) 2014 ORS abstract

F) 2012 ORS poster

G) 2013 OTA poster

H) 2014 ORS poster

I) 2012 Techniques in Orthopaedics manuscript

J) 2013 Injury manuscript

•A Canine Model for Measuring Tissue Oxygenation as a Diagnosis of Compartment Syndrome

+[1]Kang, H; [2]Mok, J; [2]Hansen, E; [2]Kandemir, U; [2]Rollins, M; [1]Manzano, G; [1,2]Liu, X; [1,2]Kim, H
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INTRODUCTION:

The diagnosis of acute compartment syndrome (CS) of the extremity – increased pressure within the osseofascial compartments, leading to blocked circulation, lack of oxygen, and tissue necrosis – has been a grey area in clinical orthopaedics. The current warning criteria, which rests on the difference between the diastolic blood pressure and compartment pressure (ΔP) in addition to primarily clinical observations, has been reported to be unreliable, resulting in a high percentage of unnecessary fasciotomy.[1]

In investigating a more objective, accurate method of identifying CS, we measured the partial pressure of oxygen of the anterolateral (AL) muscle compartment in a canine model, as a novel approach to evaluating the direct marker of the underlying pathophysiology of the pressure-induced ischemia and tissue necrosis due to CS. Decreased tissue oxygenation (PmO_2) due to reduced blood flow after CS is believed to be responsible for the tissue damage in the compartment. Continuous measurement of intramuscular PmO_2 of the leg during controlled induction of CS in an established dog model[2] has shown to be highly responsive and sensitive.

METHODS:

Animal model and PmO_2 measurement: The study included 7 female beagles. After the induction of anesthesia, compartment syndrome was induced in the anterolateral compartment of right hind legs (CS limb) by colloid fluid (Hextend®) infusion through an intramuscular angiocath to maintain a compartment pressure 30mmHg above the diastolic blood pressure (ΔP = -30mmHg) as measured by arterial line. In the contralateral positive control leg (TI limb), a tourniquet was applied over the upper leg and the pressure elevated to 300mmHg. Polarographic oxygen probes (Licox®, Integra LifeSciences) were placed percutaneously into the AL compartment of both legs to measure the PmO_2. After approximately 6 hours of compartment syndrome and tourniquet-induced ischemia, fasciotomy was performed and the tourniquet was deflated on respective legs. PmO_2 was recorded every 30 seconds on the CS limb. Animals were euthanized at the conclusion of experiments. This protocol was approved by our institutional review board.

Tissue viability: Affected AL muscle tissue from the CS limb were biopsied at different time points: 3 hours after TI (rev TI), 6 hours after TI (end TI), 1 hour after tourniquet release (post TI), 4 hours after induction of CS (end CS), and 1 hour after fasciotomy (post CS) Tissue viability was assessed with MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) according to Crawford et al.[3] The assay quantifies the reduction of a tetrazolium salt (MTT) to water-insoluble colored formazan crystals by mitochondrial enzymes of viable tissue. The absorbance of the formazan crystals at 570nm was normalized to the dry weight of the muscle sample. The tissue viability index was represented as the percentage of the normalized absorbance of affected tissue to that of negative control quadriceps tissue.

RESULTS:

The average duration of the controlled induction of compartment syndrome was 5.8 hours. Before colloid infusion, the averaged mean PmO_2 of the CS limb across 7 animals was 30.71mmHg (range 10.56-50.18mmHg), and during induced compartment syndrome, the PmO_2 decreased in all animals to an average of 1.22mmHg (range -0.06-3.65mmHg, $p<0.05$ by Wilcoxon rank sum test). Immediately before fasciotomy, the averaged mean PmO_2 was -0.17 (range -0.50-0.41mmHg), and after fasciotomy, PmO2 promptly recovered in all animals to an averaged mean of 37.08mmHg (range 2.41-90.40mmHg, $p<0.05$). In the contralateral control limb, PmO_2 decreased to 0mmHg after the application of tourniquet and promptly recovered to normal range after the release of tourniquet in all animals.

The viability indices of end TI, post TI, end CS, and post CS, but not rev TI, were significantly decreased from that of the control quadriceps tissue ($p<0.05$, Figure 2). The viability index differences between end TI and end CS and between post TI and post CS were not significant. We did not observe significant differences between end TI and post TI and between end CS and post CS, which may be due to the short recovery period of 1 hour.

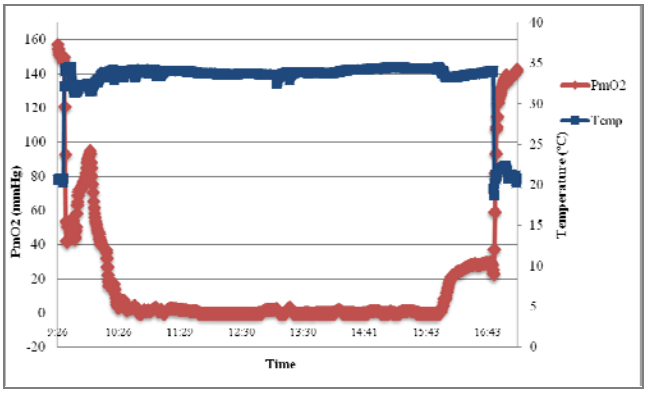

Figure 1. Representative tissue oxygenation and temperature measurement in CS limb. Probe insertion at 9:33; start of infusion at 10:03; fasciotomy at 16:01.

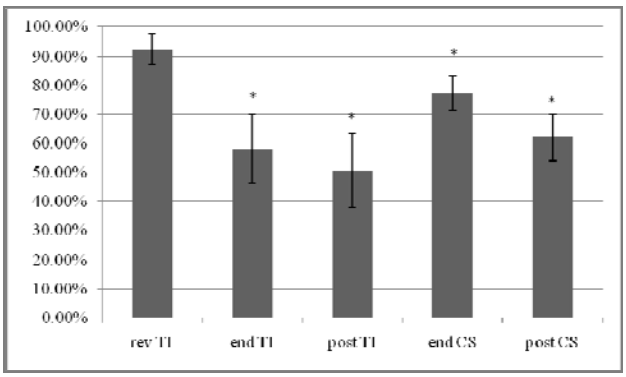

Figure 2. Tissue viability index represented as percentage of the control quadriceps tissue.

DISCUSSION:

We demonstrated that the controlled induction of compartment syndrome using an infusion method results in a substantial decrease in PmO_2, as measured by polarographic oxygen probes, and in tissue viability index, as quantified by MTT, to values similar to tourniquet-induced ischemia. PmO_2 was responsive and sensitive to changes in tissue oxygenation, as shown by the prompt recovery of PmO_2 after fasciotomy and tourniquet deflation. Therefore, measurement of intramuscular tissue oxygenation appears to detect pressure-induced ischemia in an animal model with high translational potential.

SIGNIFICANCE:

This novel model for monitoring compartment syndrome with polarographic oxygen probes may represent a minimally invasive, physiologic, continuous, and reliable method for diagnosing compartment syndrome.

ACKNOWLEDGEMENTS:

This study was supported by the Orthopaedic Surgery and Sports Medicine Teaching and Research Foundation and the Department of Defense.

REFERENCES:

1. Janzing HM, Broos PL. Injury 32(5):415-21 (2001).
2. Hargens AR et al. JBJS 63(4):631-6 (1981).
3. Crawford RS et al. Am J Phys Heart Circ Physiol 292:H830-837 (2007).

Non-operative Treatment For Compartment Syndrome With Phenylephrine and Dobutamine

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Disclosures:
X. Liu: None. **J. Mok:** None. **H. Kang:** None. **J. Jin:** None. **A. Boehme:** None. **E. Hansen:** None. **U. Kandemir:** None. **M. Rollins:** None. **H.T. Kim:** None.

Introduction: Acute compartment syndrome (CS) of the extremity describes increased pressure within the osseofascial compartment, leading to compromised circulation, hypoxia, and ultimately muscle and nerve necrosis. Current treatment for acute extremity symptomatic CS is fasciotomy. However, surgical treatment has associated morbidity and may delay the recovery of the patients. The goal of this study is to investigate the feasibility of a novel non-surgical treatment for acute compartment syndrome by increasing blood pressure using a dog CS model.[1] We hypothesize that pharmacological treatment that raises the blood pressure will improve limb perfusion and tissue oxygenation, thus rescue muscle from CS.

Methods: All procedures were approved by the Institutional Animal Care and Use Committee at ISIS Services. Under general anesthesia, CS was induced in the anterolateral compartment on bilateral legs in 10 animals (4 treated and 6 non-treated) via Hespan infusion with a goal pressure of 30mmHg above diastolic blood pressure (ΔP=-30mmHg). Polarographic oxygen measurement electrodes were placed percutaneously into the anterolateral compartment. Intramuscular tissue oxygenation, compartment pressure, and blood pressure were recorded every 30 seconds. In the treated group, pharmacological treatments begin at 1 hour after the compartment syndrome is induced. Infusion of intravenous phenylephrine was initiated at 25mcg/min and titrated up to 100mcg/min as needed to increase the diastolic blood pressure 30mmHg above the baseline(ΔP=0mmHg). Intravenous dobutamine at 60mcg/min was initiated 2 hours later. Six to seven hours after treatment, fasciotomy was performed on one leg of the animals and the skin was closed 1 hour later. In the non-treatment group, similar procedures were performed expect that neither pharmacological nor fasciotomy was performed. Animals were euthanized 2 weeks postoperatively at which point muscle biopsies were performed. Tissue viability was assessed by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as previously described.[2,3] This is a validated technique in which the normalized tissue viability index is expressed as a percentage of control (quadriceps muscle).

Results: Pharmacological treatment significantly increased PmO2 in the anterior compartment muscle. The PmO2 in the treatment group was 18.8 ± 4.3 mmHg (mean ±SE) during the experiment. In contrast, PmO2 in the non-treated group dropped to 0 mmHg soon after the compartment syndrome was induced. Fasciotomy increased the PmO2 to 35.7 ± 15mmHg. Two weeks after surgery, the muscle viability index in pharmacological treated, pharmacological plus fasciotomy and non-treated groups were 128 ± 15%, 94.3 ± 8.3%, 41.8 ± 17% (mean ± SE) respectively. There was no significant difference between pharmacological treated and pharmacological plus fasciotomy groups (P=0.09). However, both treated groups have higher tissue viability compared to the non-treated group (P<0.01) (Figure 1).

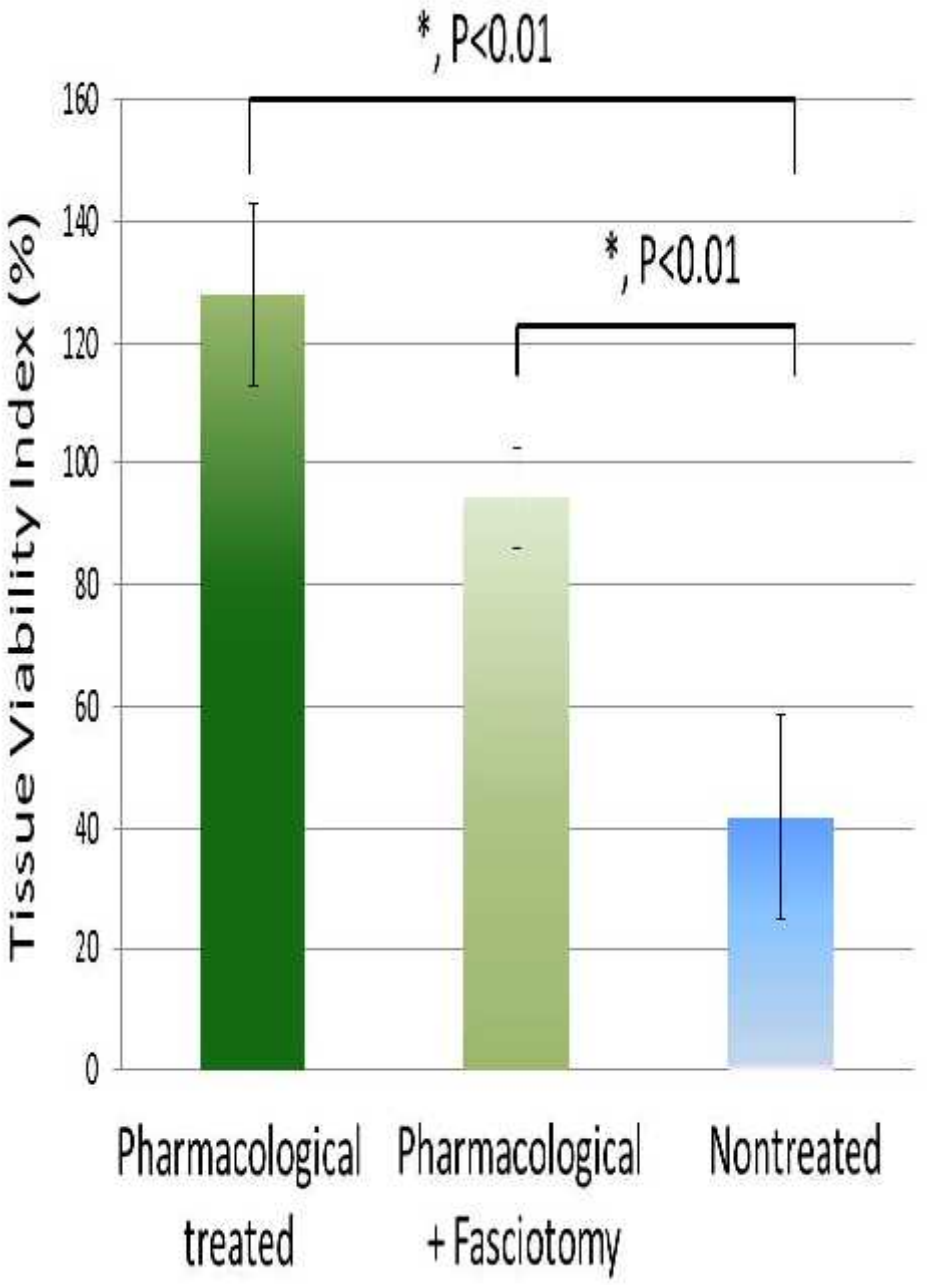
Discussion: Our results showed that non-surgical pharmacological treatment significantly increases muscle oxygen and viability and may represent an alternative, less morbid treatment for acute compartment syndrome than fasciotomy. Phenylephrine is often used for trauma patients in the perioperative setting to maintain blood pressure and could serve as initial therapy in patients with possible compartment syndrome. However, in our study, the effect of phenylephrine decreased over time, and a second line drug (dobutamine) was needed after the first few hours. We are currently testing this treatment strategy in more animals. Future works include titrating drug dosing, long-term effect follow up, muscle histology and functional analysis.

Significance: Keeping the blood pressure at a high level using pharmacological agents (phenylephrine/dobutamine combination) may serve as an alternative to surgical treatment for acute compartment syndrome.

Acknowledgments: This study was supported by the Department of Defense (Grant Number: W81XWH-10-1-1024).

References: 1. Hargens AR et al. J Bone Joint Surg 1981;63(4):631-6.

2. Bonheur JA et al. J Surg Res 2004;116:55-63.
3. Crawford RS et al. Am J Physiol Heart



ORS 2014 Annual Meeting
Poster No: 1086

A Canine Model for Measuring Tissue Oxygenation as a Diagnosis of Compartment Syndrome

[1]Kang, H; [2]Mok, J; [2]Hansen, E; [2]Kandemir, U; [2]Rollins, M; [1]Manzano, G; [1,2]Liu, X; [1,2]Kim, H

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Introduction

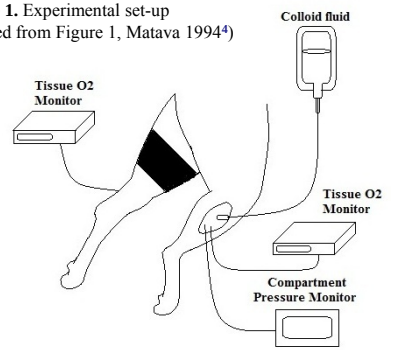
Acute compartment syndrome (CS) of the extremity is characterized by increased pressure within the fascial compartments, leading to blocked circulation, lack of oxygen, and tissue necrosis. The current standard diagnostic criteria, which is primarily based on a combination of clinical symptoms and needle measurement of ΔP (difference between the diastolic blood pressure and compartment pressure), have been reported to be unreliable, resulting in a high percentage of unnecessary fasciotomy.[3]

As a novel approach to objectively diagnosing CS, the partial pressure of oxygen of the anterolateral (AL) compartment was measured in a dog model. Monitoring tissue oxygenation (PmO2) allows for the evaluation of the direct marker for the underlying pathophysiology of the pressure-induced ischemia and tissue necrosis due to CS. Continuous measurement of intramuscular PmO2 of the leg during controlled induction of CS in an established dog model[2] has shown to be highly responsive and sensitive.

Methods

Animal model and PmO2 measurement: The study included 7 female beagles. After the induction of anesthesia, polarographic oxygen probes (Licox, Integra LifeSciences) were placed percutaneously into the AL compartment of both legs to measure the PmO2. CS was induced in the AL compartment of the right hind legs (CS leg) by colloid fluid infusion through an intramuscular catheter to maintain a compartment pressure 30mmHg above the diastolic blood pressure (ΔP=-30mmHg) as measured by the arterial line. Tourniquet ischemia was induced as a positive control in the contralateral leg (TI leg) by applying a tourniquet over the upper leg and elevating the pressure to 300mmHg. After 6 hours, fasciotomy was performed on the CS leg and the tourniquet was deflated on the TI leg. PmO2 was recorded every 30 seconds. Animals were euthanized at the conclusion of the experiment. This protocol was approved by the UCSF Institutional Animal Care and Use Committee.

Figure 1. Experimental set-up (adapted from Figure 1, Matava 1994[4])



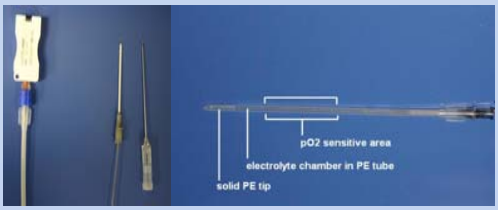


Figure 2. Polarographic oxygen probe.

Tissue viability: Affected AL muscle tissues were biopsied at different time points: 4 hours after TI (rev TI), 6 hours after TI (end TI), 1 hour after tourniquet release (post TI), 6 hours after induction of CS (end CS), and 1 hour after fasciotomy (post CS). Tissue viability was assessed with MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) according to Crawford et al.[1] The tissue viability index is represented as the percentage of the absorbance of affected tissue to that of negative control quadriceps tissue, normalized to dry weight.

Results

The average duration of the controlled induction of CS was 5.8 hours. Before colloid infusion, the averaged mean PmO2 of the CS limb across 7 animals was 30.71mmHg (range 10.56-50.18mmHg). During induced CS, the PmO2 decreased in all animals to an average of 1.22mmHg (range -0.06-3.65mmHg, $p<0.05$ by Wilcoxon rank-sum test). Immediately before fasciotomy, the averaged mean PmO2 was -0.17 (range -0.50-0.41mmHg). After fasciotomy, PmO2 promptly recovered to an averaged mean of 37.08mmHg (range 2.41-90.40mmHg, $p<0.05$) In the contralateral TI limb, PmO2 decreased to 0mmHg after the application of tourniquet and recovered to normal range after release.

Tissue Oxygenation Measurement in CS Leg

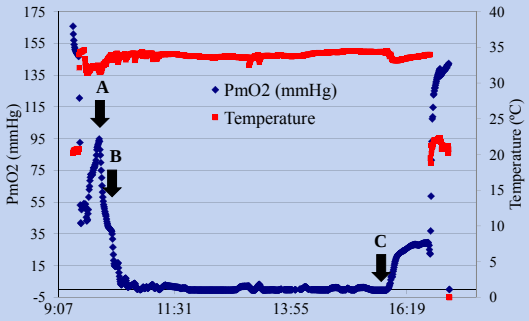


Figure 3. Representative tissue oxygenation and temperature measurements in CS leg. **A**. Probe insertion at 9:33; **B**. Start of infusion at 10:03; **C**. Fasciotomy at 16:01.

The viability indices of end TI, post TI, end CS, and post CS, but not rev TI, were significantly reduced from that of the control quadriceps tissue ($p<0.05$, Figure 4).

Tissue Viability Index Normalized to Control

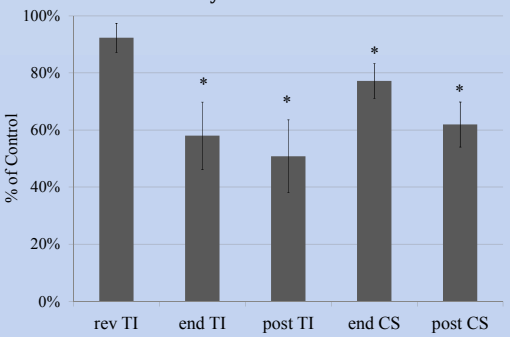


Figure 4. Tissue viability index represented as percentage of negative control. (*rev TI* = 4h tourniquet ischemia; *end TI* = 6h tourniquet ischemia; *post TI* = 1h after tourniquet deflation; *end CS* = 6h CS; *post CS* = 1h after fasciotomy)
* $p<0.05$ compared to control

Discussion

We demonstrated that the controlled induction of compartment syndrome using an infusion method results in a substantial decrease in PmO2, as measured by polarographic oxygen probes, and in tissue viability index, as quantified by MTT, to values similar to tourniquet-induced ischemia. PmO2 was responsive and sensitive to changes in tissue oxygenation, as shown by the prompt recovery of PmO2 after fasciotomy and tourniquet deflation. Therefore, a measurement of intramuscular tissue oxygenation appears to detect pressure-induced ischemia in an animal model with high translational potential.

This novel model for monitoring compartment syndrome with polarographic oxygen probes may represent a minimally invasive, physiologic, and reliable method for diagnosing compartment syndrome.

Acknowledgements

This study was supported by the Orthopaedic Surgery and Sports Medicine Teaching and Research Foundation and the Department of Defense (OR090580).

References

[1] Crawford RS et al. Am J Physiol Heart Circ Physiol 292(2):H 830-7 (2007)
[2] Hargens AR et al. JBJS 63(4):631-6 (1981)
[3] Janzing HM, Broos PL. Injury 32(5):415-21 (2001)
[4] Matava MJ et al. J Trauma 37(1):50-8 (1994)

Relationship of Intramuscular Tissue Oxygenation and Muscle Viability in a Compartment Syndrome Model

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THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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INTRODUCTION

Diagnosis of acute compartment syndrome (CS) remains problematic due to lack of objective criteria to measure viability of muscular tissue.

We have previously shown that continuous measurement of intramuscular tissue oxygenation (PmO2) of the leg is:

- feasible in humans. (Hansen *Injury* 2013)
- highly responsive to induced compartment syndrome and fasciotomy in a dog model. (Mok *AAOS* 2012)

Using the same model, we investigated the relationship between PmO2 after fasciotomy and biochemical measurements of tissue viability.

METHODS

Under general anesthesia, CS was induced in the anterolateral compartment of one leg in 4 animals via Hespan infusion with a goal pressure 30mmHg *above* diastolic blood pressure.

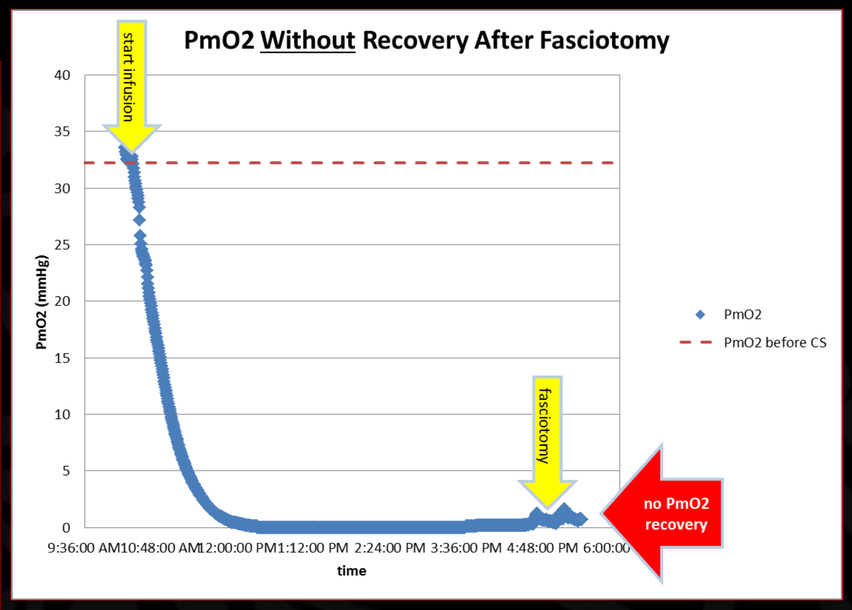
Polarographic oxygen probes (Fig. 1) were placed percutaneously into the anterolateral compartment. (Fig. 2)

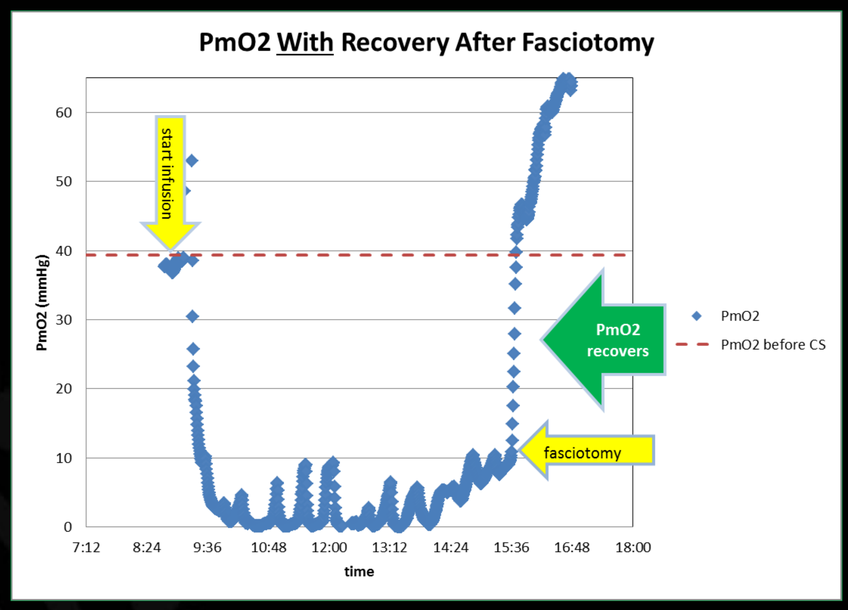
PmO2 was recorded every 30 seconds.

After approximately 7 hours of compartment syndrome, fasciotomy was performed**.**

Animals were euthanized 2 weeks postoperatively at which point muscle biopsies were performed. Control was quadriceps (unaffected by CS).

Tissue viability was assessed by histologic analysis (H&E, Masson's trichrome, cytochrome c oxidase stains) and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, in which viability is expressed as a percentage of control.





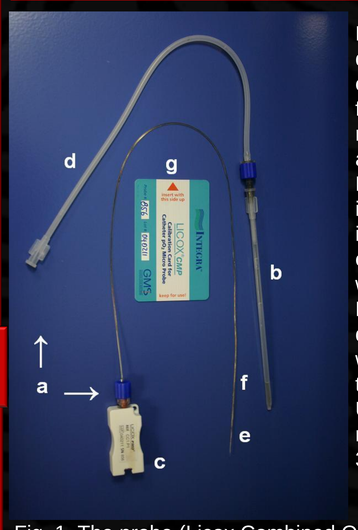


Fig. 3 (above). Left: PmO2 decreases with induction of CS. Following fasciotomy, it did not recover. MTT in this animal was 10.78%. Right: PmO2 decreased with induction. Intermittent increases of PmO2 were observed but decreased with additional infusion of Hespan to maintain goal deltaP. During CS, PmO2 was substantially lower than PmO2 before CS. Upon fasciotomy, PmO2 recovered. MTT was 35.7%.

Fig. 1. The probe (Licox Combined Oxygen and Temperature Probe CC1.P1, Integra, Plainsboro, NJ) is a Clark type polarographic oxygen probe (e) and temperature measurement (f) device and comes packaged as shown: (a) probe enters the extension tube (d) and plastic closed humid chamber over the tip (b). The plastic cover (b) is removed for insertion. The probe is connected to the monitor via a cable at (c). A smart card with calibration data specific to each probe is inserted into the monitor. Letter (e) shows the oxygen sensitive area and (f) shows the temperature sensitive area of the probe.

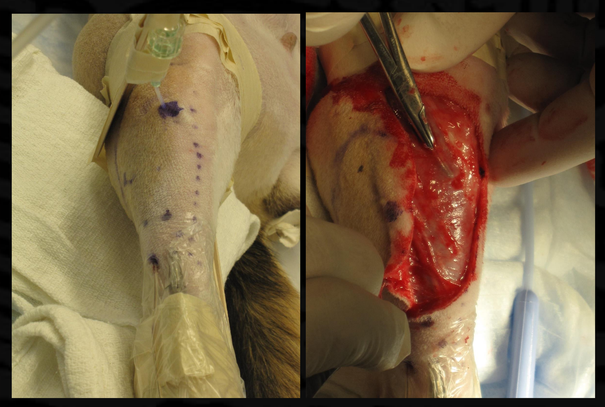


Fig. 2. Left: Probe placement in right leg. Animal is supine. Infusion catheter is green angiocath at top. Angiocath for compartment pressure measurement is bottom left. 1 cm adjacent and parallel, on bottom right, is oxygen probe. Both placed percutaneously. Right: Fasciotomy. Instrument between fascia and underlying muscle. Skin flap is closed after fasciotomy.

RESULTS

Mean duration of CS was 6.9 hours.

Pre-CS averaged mean PmO2 (n=4) was **35.63mmHg (15.22-53.65)**.

This decreased to **2.54mmHg (0.19-4.92)** during induced CS (p=0.06).

Following fasciotomy, **2** animals showed recovery exceeding a threshold PmO2 of 10mmHg. **2** animals did not. (Fig. 3)

At 2 weeks, animals with persistent low PmO2 (n=2) had:

- **Significantly more fibrosis on histologic analysis (collagen fiber:muscle tissue ratio 45.58% vs. 21.98%, p=0.01)**
- **Lower viability index (9.23% vs. 44.41%, p=0.1)**

CONCLUSIONS

PmO2 values following fasciotomy appear to reflect underlying muscle viability as confirmed by histologic methods using a previously suggested threshold PmO2 (10mmHg). This is an important finding if PmO2 is to be used to guide the treatment of CS.

Measurement of intramuscular tissue oxygenation detects pressure-induced ischemia and may predict irreversible necrosis in an animal model with high translational potential. It may represent a minimally invasive, physiologic, and continuous method for diagnosing compartment syndrome.

Non-operative Treatment of Compartment Syndrome with Phenylephrine and Dobutamine

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Introduction

Acute compartment syndrome (CS) of the extremity describes increased pressure within the osseofascial compartment, most commonly stemming from trauma to the extremity. Increasing pressure in the compartment results in compromised circulation, hypoxia, and ultimately muscle and nerve necrosis.

Current treatment for acute extremity symptomatic CS is fasciotomy. However, surgical treatment has associated morbidity and may delay patient recovery. Restoring perfusion to the affected compartment through less invasive methods could improve treatment outcomes.

Goals: The goal of this study is to investigate the feasibility of a novel non-surgical treatment for acute compartment syndrome by increasing systemic blood pressure in a dog CS model.

Hypothesis: We hypothesize that pharmacological treatment with hypertensive drugs will raise blood pressure, improve limb perfusion, and increase tissue oxygenation, thus rescuing the muscle from CS.

Methods

- Compartment syndrome was induced in the anterolateral compartment on bilateral hind legs in 12 animals (6 treated and 6 non-treated) via Hespan infusion.
- Intramuscular tissue oxygenation, compartment pressure, and blood pressure were recorded every 30 seconds.
- In the treated group (n=6), pharmacological treatments began 1 hour after compartment syndrome was induced. Phenylephrine was administered intravenously to increase diastolic blood pressure. Dobutamine was initiated two hours later. After six to seven hours of CS, fasciotomy was performed on one leg. No fasciotomy was performed on the contralateral leg (served as drugs-only treatment).
- In the untreated group (n=6), identical CS conditions were induced but without rescue from either pharmacological interventions or fasciotomy.
- Animals were euthanized 2 weeks postoperatively, at which point muscle biopsies were harvested.

  --Tissue viability was measured with the MTT assay.

  --Samples were stained with Hematoxylin & Eosin and Masson's Trichrome for histological analysis.

Results

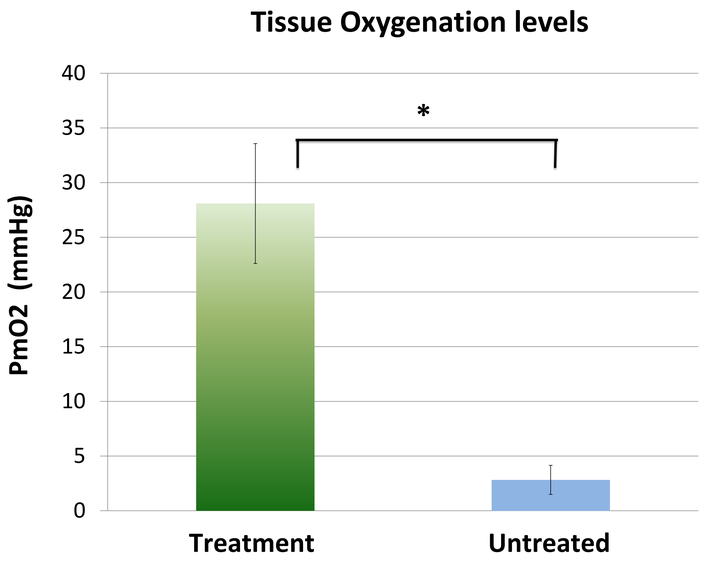

Figure 1: Tissue oxygenation levels were significantly higher in treated animals (n=12) compared to untreated controls (n=6). Treated animals had an average PmO2 = 28.1 +/- 5.6 mmHg over the 7 hours of CS and untreated had PmO2 = 2.82 +/- 1.3 (*=p< 0.01). There was no difference in PmO2 between the two treatment groups.

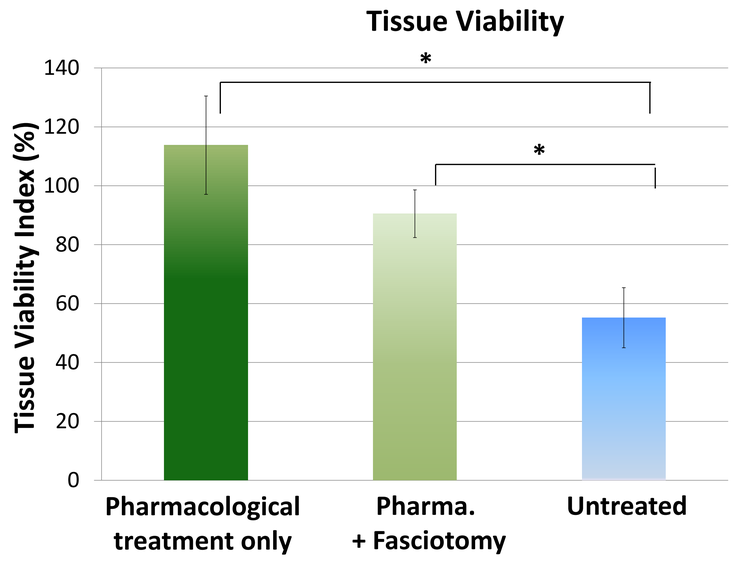

Figure 2: Muscle viability after treatment with drugs-only and drugs +fasciotomy was compared with untreated controls. There was no significant difference in tissue viability between the two treatment groups (113 +/- 16.7% for drugs-only and 90 +/- 8.1% for drugs + fasciotomy). Both treated groups showed increased viability compared to the untreated controls (* = p <0.03).

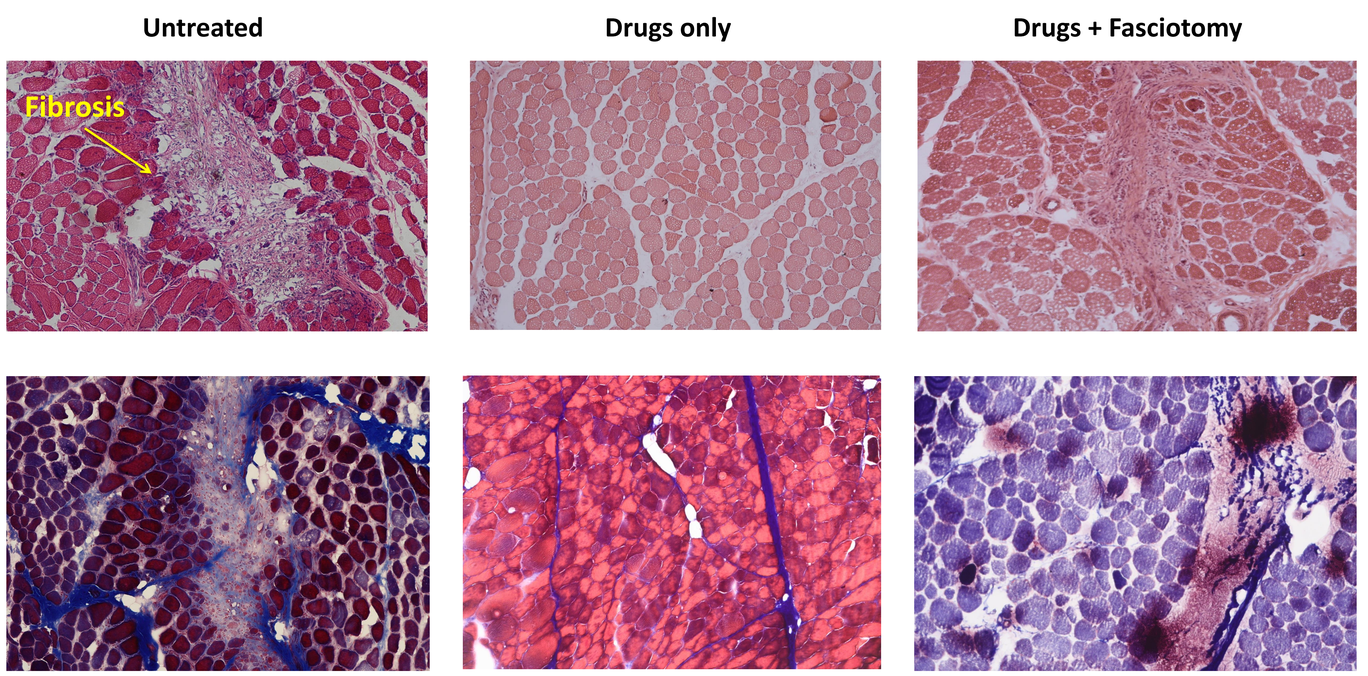

Figure 3: Muscle histology H & E (top) and Masson's Trichrome (below) showed that untreated dogs had a greater degree of muscle damage and fibrosis than dogs treated with drugs only or drugs + fasciotomy.

Discussion

Our results showed that non-surgical pharmacological treatment significantly increases muscle oxygen and viability and may represent an alternative, less morbid treatment for acute compartment syndrome than fasciotomy.

Phenylephrine is often used for trauma patients in the perioperative setting to maintain blood pressure ,and could serve as an initial therapy in patients with possible CS.

However, in our study, the effect of phenylephrine decreased over time, and a second line drug (dobutamine) was needed after the first few hours. Future works include titrating drug dosing, long-term effect follow up, and functional analysis.

Significance

Keeping the blood pressure at a high level using pharmacological agents (Phenylephrine/dobutamine combination) may serve as an alternative to surgical treatment for acute compartment syndrome.

Acknowledgments

This study was supported by the Department of Defense (Grant Number: W81XWH-10-1-1024).

Diagnosis of Acute Compartment Syndrome: Direct Measurement of Tissue Oxygenation

James Moon Mok, MD, Erik N. Hansen, MD,† Heejae Kang, BS,† and Utku Kandemir, MD†*

Summary: We present a technique and feasibility study of continuous measurement of intramuscular tissue oxygenation as a potential novel approach to the diagnosis of acute extremity compartment syndrome. Polarographic probes were inserted percutaneously into the anterior compartment of the leg to measure the partial pressure of oxygen (PmO_2). Five patients underwent open reduction internal fixation of ankle fracture under a thigh tourniquet. With application of the tourniquet, the mean PmO_2 decreased rapidly from 26.62 to 0.52 mm Hg (range, 0.1 to 1.4 mm Hg). Eleven patients underwent monitoring of tissue oxygenation after intramedullary nailing for an isolated closed tibia fracture. No compartment syndrome occurred. In the absence of compartment syndrome, 1.35% of PmO_2 measurements spanning 424 hours fulfilled the predefined warning criterion of $PmO_2 < 10$ mm Hg. Our data establish the feasibility of measuring tissue oxygenation and its responsiveness to ischemia. In contrast to compartment pressure, PmO_2 measurements after tibia fracture rarely fulfilled the warning criterion in the absence of compartment syndrome. A floor PmO_2 value of nearly zero was established in live ischemic muscle. Tissue oxygenation may represent a minimally invasive, physiologic, and specific method for diagnosing compartment syndrome.

Key Words: compartment syndrome—compartment syndrome diagnosis—intramuscular tissue oxygenation.

(*Tech Orthop* 2012;27: 22–29)

Acute compartment syndrome describes the elevation of pressure within the nonyielding fascial compartments of the extremities, leading to compromise of circulation, local ischemia, and ultimately tissue necrosis. This potentially devastating sequela of lower extremity trauma is estimated to occur in up to 10% to 20% of patients sustaining a tibia fracture.[1,2] Delay in diagnosis or treatment may have catastrophic consequences, including permanent neurological deficit, infection, delayed union, loss of function, and amputation. Therefore, a timely and accurate diagnosis is imperative. The main objective test in current use is measurement of compartment pressure. However, considerable controversy exists with regard to thresholds for fasciotomy,[3–5] which has resulted in problematic clinical ambiguity.

Because the pathophysiology of compartment syndrome involves pressure-induced ischemia of the muscle, monitoring of tissue oxygenation represents an intuitive strategy for diagnosis. Near-infrared spectroscopy (NIRS) is a transcutaneous method of measurement that has recently been the subject of interest. Studies evaluating NIRS for both chronic and acute compartment syndrome have revealed merits in measuring tissue oxygenation in these settings.[6] The clinical application of NIRS has been limited by qualities inherent to the device itself, and difficulties with reliability and reproducibility.[7]

The use of an intramuscular tissue probe to directly measure the partial pressure of oxygen (PmO_2) may be a reliable method of assessing tissue oxygenation. The probe used for this method is a polarographic oxygen probe approved by the US Food and Drug Administration for monitoring brain tissue oxygenation. This probe has been studied for applications within skeletal muscle in the critical care and plastic surgery literature and has been found to be highly responsive to changes in oxygenation.[8–10] Several authors have suggested that PmO_2 of 10 mm Hg may represent a critical threshold for irreversible muscle ischemia.[11–13]

The purpose of this paper is to describe a technique for the measurement of intramuscular tissue oxygenation in the anterior compartment of the leg using a specific probe. We investigate the feasibility of this technique as a novel approach to the diagnosis of compartment syndrome. Continuous measurement of PmO_2 in human leg muscle was performed in 2 clinical conditions of altered lower extremity perfusion. In the first part, we sought to validate the responsiveness and sensitivity of the probe to tourniquet ischemia in patients undergoing an elective ankle fracture surgery and establish a floor value of skeletal muscle ischemia. In the second part, we measured continuous intramuscular tissue oxygenation of the leg in the postoperative setting in patients who underwent intramedullary nailing of a tibia shaft fracture. This group was considered at risk for developing a compartment syndrome. The number of measurements meeting the predefined warning criterion for critical tissue oxygenation was determined.

MATERIALS AND METHODS

Probe

The tissue oxygenation probe used (Licox Combined Oxygen and Temperature Probe CC1.P1, Integra, Plainsboro, NJ) is a Clark-type polarographic oxygen probe and temperature measurement system that utilizes an electrochemical microcell for oxygen sensing, which is expressed as the partial pressure of oxygen in muscle (PmO_2; Fig. 1). A Clark-type electrode consists of a cathode and an anode connected through an electrolyte solution and covered with an oxygen-permeable membrane. An external voltage source is used to

Received for publication December 14, 2011; accepted December 27, 2011.

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E.N.H. received a grant from the Orthopaedic Trauma Association for this work.

The views expressed are those of the authors and do not reflect the official policy or position of the US Army, Department of Defense or the US Government.

The authors declare that they have nothing to disclose.

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ISSN: 0148-703/12/2701-0022

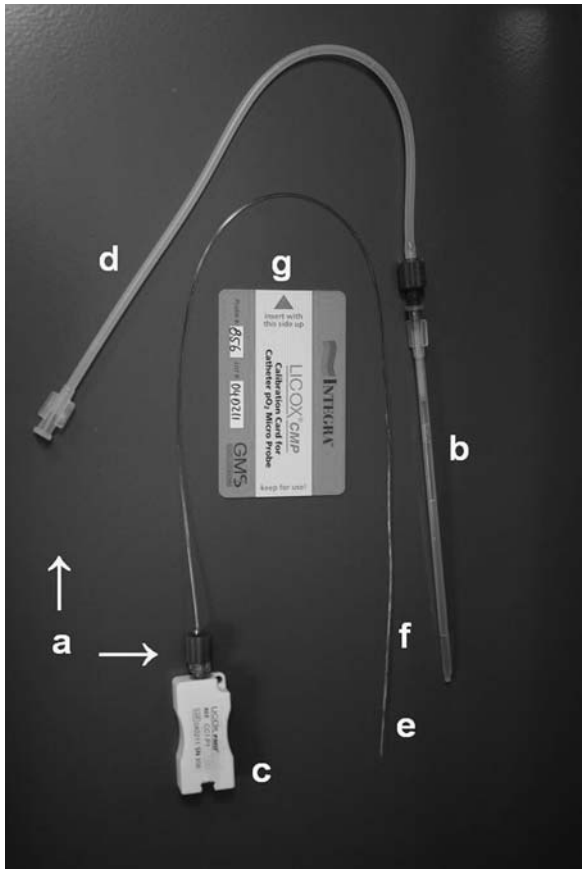

FIGURE 1. The probe comes packaged with the components as shown. Letter (a) depicts where the probe enters the extension tube (d) and plastic closed humid chamber over the tip (b). The plastic cover (b) is removed to allow calibration with room air and for insertion. The probe is connected to the monitor through a cable at (c). A smart card with calibration data specific to each probe is inserted into the monitor. Letter (e) shows the oxygen-sensitive area and (f) shows the temperature-sensitive area of the probe.

make the cathode slightly negatively charged relative to the anode. Dissolved oxygen in the tissue is reduced at the cathode to OH ions, which produces a measureable current.[14] Because cell membranes do not represent an O_2 diffusion barrier and because the diffusion distance between the interstitial space and the mitochondria is short, the PmO_2 in tissue is assumed to correspond to that available at the cellular level.[15] The current from the O_2 reduction is the raw signal of the sensors, which are located on a 2-cm segment at the tip of the probe. All sensors must be in tissue to obtain correct readings. Because the reactions in the probe are reversible, measurements are stable and continuous.[15] The current varies depending on the temperature, even if the PmO_2 in the environment remains constant. The change in probe PmO_2 sensitivity with a change in temperature is approximately 4%/°C.

The probe is 0.8 mm in diameter and can be inserted into muscle percutaneously. It is a single-use disposable item. It is handled under sterile conditions and connected to a proprietary monitor (Licox CMP instrument, Integra, Plainsboro, NJ) through an electrical cable. The monitor can be connected to a computer through an interface cable to record oxygen and temperature data at user-defined intervals.

Technique

After removal from its packaging, the probe is connected to the monitor and allowed to calibrate to room air (154 mm Hg O_2) before insertion in the patient. Attention should be paid to ensure that the probe tip does not dry out. Before placement of the catheter, the probe is marked from its tip to the entire length of the catheter, including the plastic hub (Fig. 2A). This facilitates advancement of the probe up to, but not exceeding, the length of the catheter. The probe is placed percutaneously under sterile conditions using a modified Seldinger technique. After sterile preparation of the leg and with the patient under anesthesia, a 14 G, 6-cm length intravenous catheter is placed in the anterior compartment of the leg approximately 2 cm lateral and 5 cm distal to the tibial tubercle (Fig. 2B). These distances may be adjusted depending on the size of the leg and the fracture location. The catheter is oriented longitudinally in line with the muscle fibers, pointing distally, and inserted at an oblique angle to the skin surface of approximately 20 degrees to ensure intramuscular placement. Excessively deep penetration should be avoided to remain in the compartment and protect the neurovascular bundle. The catheter is inserted to its entire length. Initial probe placements were confirmed to be within the anterior compartment by ultrasound. Atraumatic placement is mandatory and is confirmed by the absence of back bleeding after removal of the needle from the catheter (Fig. 2C).

After the needle is removed from the catheter, the probe is then placed through the catheter up to the previously placed mark (Fig. 2D). The catheter is slowly and carefully withdrawn from the patient while maintaining the probe's location in the muscle (Fig. 2E). If the probe is advanced too far, its delicate tip will be kinked. If it is advanced too short, it will remain within the tract created by the catheter. The probe is sufficiently long for the catheter to be completely withdrawn from the patient and then screwed into the male blue Luer taper at the proximal end of the probe. The mark on the probe should be visible at the skin surface to confirm that it has been advanced to the intended length.

The probe is then secured to the patient. This must be approached carefully because probe dislodgment frequently occurs during this step. Any folding or kinking of the probe will render it nonfunctional. A transparent dressing (Tegaderm, 3M, St Paul, MN) is used to secure the probe to the skin at the puncture site. Proximal to this, a hydrocolloid dressing (DuoDerm, ConvaTec, Skillman, NJ) is placed on the skin surface between the skin and the Luer taper and extension tubing of the probe to protect it from pressure. Additional transparent dressing is generously placed over the catheter, probe, and hydrocolloid dressing to secure it to the patient. The probe can be left in place for 5 days as per the product insert (Fig. 3).

Equilibration Times and Normal Values

In our experience, calibration to room air takes approximately 10 minutes. After insertion, the PmO_2 decreases rapidly and attains a stable value in 10 to 20 minutes. Other authors have recommended an equilibration time of 20 minutes outside the body[14] and a stabilization time of 10 to 90 minutes within muscle.[9] According to the product literature of the manufacturer, a stabilization time of 20 minutes is adequate, although readings may take 2 hours to stabilize.

We considered the PmO_2 measurement to be stable when the value did not change (ie, decrease) for 5 minutes and approximated the normal range for muscle.

Normal values in muscle have been stated as 25 to 35 mm Hg.[15] An additional source of reference is a study of critically

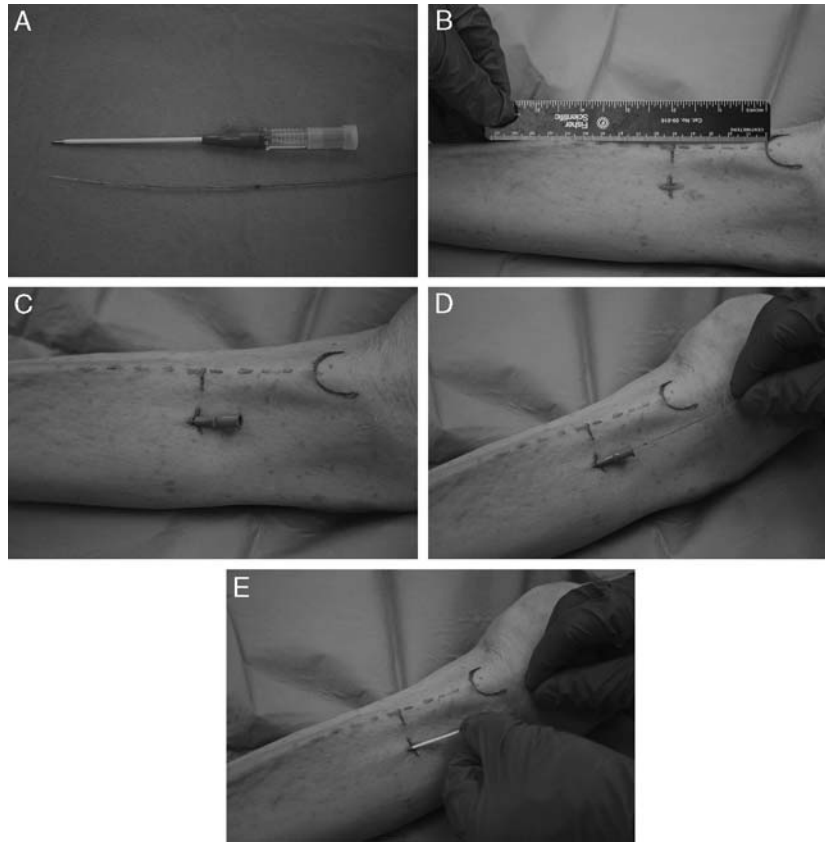

FIGURE 2. Technique for intramuscular placement of probe. (A) The probe has been marked the entire length of the catheter from its tip. During insertion of the probe, the mark should remain visible at the edge of the plastic hub of the catheter. (B) Depiction of probe placement into the anterior compartment of the left leg in a cadaver. Suggested placement is 5 cm distal and 2 cm lateral to the tibial tubercle. (C) The catheter is inserted its entire length and no back bleeding is confirmed after removal of the needle. (D) The probe is inserted into the catheter. Determination of the depth of insertion is facilitated by the previously placed mark. (E) The catheter is carefully removed while maintaining the probe position and depth.

injured ICU patients at our institution. The deltoid muscle was monitored using this technique in 27 patients for a mean of 3.2 days (unpublished data), and PmO_2 was recorded every minute. The mean PmO_2 was 34.78 mm Hg with a SD of 11.41. Most patients were intubated (mean FiO_2 52.3%), which may make these PmO_2 values higher than normal. Of 114,644 measurements in 27 patients, 0.5% were 11 mm Hg or below, which also supports the hypothesis that $PmO_2 < 10$ mm Hg is abnormal.[11–13]

According to the product literature of the manufacturer, the accuracy of PmO_2 measurement at 37°C is within 2 mm Hg for a PmO_2 of 0 to 20 mm Hg, 10% for a PmO_2 of 21 to 50 mm Hg, and 13% for a PmO_2 of 51 to 150 mm Hg.

Pearls and Pitfalls

Because the probe was not designed specifically for intramuscular tissue oxygenation monitoring, placement and use can be challenging and labor intensive. Placement usually requires 2 persons: one person inserts the probe and maintains sterile conditions, whereas the other person connects the probe to the monitor and confirms appropriate functioning. The monitor and computer are bulky, and patient transportation can be tedious. There is no alarm function that can provide notification of a specified warning value. The probe does have its own power source and can be disconnected and reconnected to the monitor without recalibration in air, thus allowing patient mobilization for therapy while the probe remains in situ. Common problems encountered include the following:

Probe Malfunction: The probe tip is fragile, and kinking of the probe renders readings unreliable. It is essential that the probe not be advanced farther than the length of the catheter. If resistance is encountered during probe placement, there is a high risk that the tip has been kinked. Probe functionality can be confirmed only by removing the probe from the patient and observing a reading of 154 mm Hg in room air. However, reinsertion would require intramuscular placement of an intravenous catheter, which may be problematic if the patient is awake and no longer anesthetized.

Immediately after probe placement, PmO_2 readings are expected to decrease rapidly to a stable value (see normal values above). Signs of possible probe malfunction, kinking, or misplacement are PmO_2 readings that are too low and/or continue to decrease slowly to 0 mm Hg. Temperature readings, which are also provided by the probe, can be helpful. A properly functioning probe should show the ambient room temperature before placement and, after placement, should rapidly increase to match the patient's body temperature. An additional confirmatory test of probe functionality is the oxygen challenge. Increasing the rate of oxygen flow to a nasal cannula or a face mask or increasing the FiO_2 (if the patient is

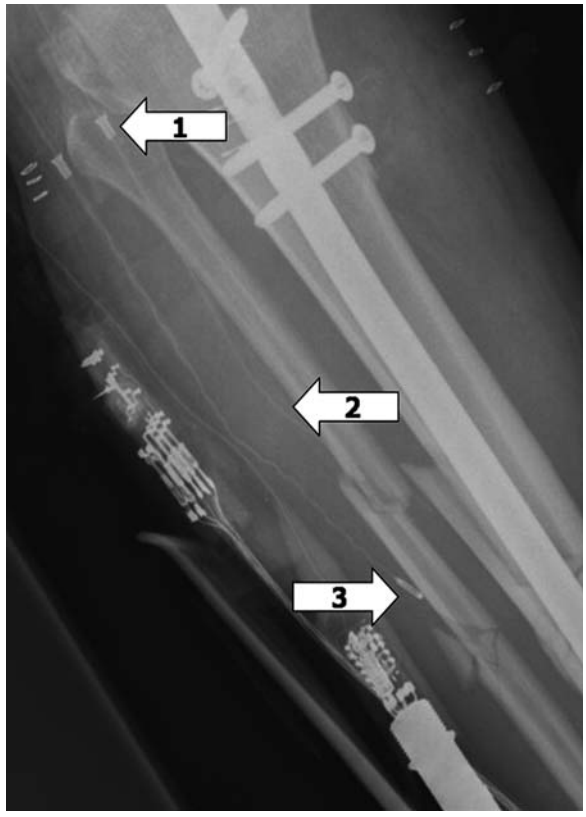

FIGURE 3. Radiographic appearance of intramuscular probe placement in the anterior compartment after intramedullary nailing for tibia fracture. The intravenous catheter tubing, which has been secured to the Luer taper, is designated by arrow 1. Arrow 2 shows the tissue oxygenation probe. Arrow 3 shows a compartment pressure probe that was placed concomitantly.

intubated) is expected to result in an increase in PmO_2 within several minutes.

Probe Misplacement: Placement of the probe into a hematoma will result in low readings, often approximating 0 mm Hg, because of the low PmO_2 within the hematoma. In contrast to compartment pressure monitoring, avoidance of the fracture site is recommended. Probe placement should be planned for areas of relatively less muscle damage. Back bleeding after placement of the catheter may indicate placement within hematoma and, if observed, the catheter should be removed and placed in a different location.

Probe Dislodgement: The probe must be well secured with special focus on the skin insertion site because this is the area where it is frequently dislodged. With prolonged monitoring and/or the presence of postoperative dressings and splints, the risk of a pressure ulcer must be recognized. The skin may be protected with a hydrocolloid dressing.

Feasibility Study

The feasibility study is a prospective observational study with 2 parts. We chose to study the anterior compartment of the leg because it is most frequently affected by compartment syndrome.[1,16] The first part included patients undergoing an elective ankle fracture surgery that required the use of a tourniquet. Continuous measurement of PmO_2 was performed to determine its responsiveness to tourniquet-induced ischemia. In the second part, patients who underwent surgery for a tibia fracture with intramedullary nailing received continuous measurements of PmO_2 postoperatively. The patient and treating nurses and physicians were blinded to the PmO_2 measurements, which were placed in a locked box at the patient's bedside.

Patient Selection and Procedures

For the first part, the inclusion criterion was patients at least 18 years of age undergoing elective open reduction internal fixation for closed ankle fracture under a tourniquet. Surgery was usually performed within 2 weeks of injury and at least 48 hours after injury on an outpatient (come and go) basis. A thigh tourniquet placed over webril was used. The tissue oxygenation probe was placed in the anterior compartment of the operative leg, whereas the patient was under anesthesia after sterile surgical prep and before the use of the tourniquet proximal to the surgical site. Tourniquet pressure was 300 mm Hg. Elevation for exsanguination was performed to minimize the risk of probe dislodgement with esmarching. The probe remained in the leg after the tourniquet was deflated and was removed as the postsurgical dressing was applied. A sterile band aid was placed over the probe insertion site.

For the second part, the inclusion criteria were as follows: patients at least 18 years of age who were admitted from the Emergency Department for treatment of a unilateral closed acute tibial shaft fracture, ability to give informed consent, and willingness to participate. The exclusion criteria were as follows: inability to give consent due to intoxication, or head injury, patients with open tibia fracture, bilateral tibia fractures, tibial plateau or plafond fracture, ipsilateral femur or pelvis fracture impending/established acute compartment syndrome, or refusal to participate. Bilateral injuries were excluded because it precluded the ability to obtain control data from the contralateral limb. Open fractures were excluded because of the potential difficulty in placing the probes percutaneously without violating open wounds and risking contamination. Only tibial shaft fractures amenable to intramedullary nail fixation were included to avoid the surgical incisions necessary for open reduction internal fixation. Both injured and well legs were subjected to surgical prep. While under anesthesia, the tissue oxygenation probe was placed in the uninjured (well) leg. PmO_2 was recorded continuously from the well leg, whereas intramedullary nailing was performed on the contralateral injured leg. After surgery was completed, sterile conditions were maintained, and the probe was removed from the well leg and placed in the injured leg. A sterile band aid was placed over the probe insertion site on the well leg. The injured leg was then placed in a removable walking boot.

Continuous monitoring of PmO_2 was performed for approximately 48 hours postoperatively, except during transport and therapy. At the conclusion of the data collection period, the probe was removed from the patient and a sterile band aid was placed over the probe insertion site on the injured leg.

Institutional review board approval was obtained for this study. All patients in both parts gave their informed consent for participation.

Data Collection and Analysis

Tourniquet Ischemia

Age, sex, type of surgery, and tourniquet time were recorded for patients in the control arm. PmO_2 measurements were recorded starting 3 minutes after insertion of the probe into the anterior compartment muscle to allow time for

calibration. PmO_2 measurements were recorded automatically every 20 or 30 seconds.

During tourniquet use, a decrease in PmO_2 was expected on the basis of the previous literature. Tourniquet ischemia PmO_2 was determined retrospectively as the stable PmO_2 (< 1 mm Hg variation) attained after the decrease. The mean ischemia PmO_2 value and the time to reach this value after tourniquet use were recorded.

Tibia Fracture

Age, sex, and mechanism of injury were recorded for patients in the experimental arm. All patients underwent intramedullary nailing of a tibial shaft fracture. PmO_2 was recorded every 20 to 30 seconds starting 15 minutes after insertion of the tissue oxygenation probe. After surgery was completed, the tissue oxygenation probes were placed in the injured leg and measurements were recorded in the same manner as above.

Warning Criteria

The number of measurements meeting the prospectively defined warning criterion of $PmO_2 < 10$ mm Hg was determined. This is a value suggested in the plastic surgery literature examining the use of the specific tissue oxygenation probe for monitoring of free flaps.[12,15]

RESULTS

No probe-related complications occurred. Probes were well tolerated by awake patients in the tibia fracture group. Probes were easily removed from these patients with minimal discomfort.

Tourniquet Ischemia

Five patients were included (Table 1). The mean age was 39.4 years. All underwent open reduction and internal fixation of a closed ankle fracture. The mean tourniquet time was 81 minutes (range, 70 to 114 min). The average of each patient's mean pretourniquet PmO_2 was 26.62 mm Hg (SD 11.03). This value is similar to previously reported PmO_2 values in the literature.[8–10,17,18]

In all 5 patients, shortly after the use of a tourniquet, a rapid decrease in PmO_2 was observed before stabilizing at a substantially lower value (Fig. 4). The mean tourniquet ischemia PmO_2 was 0.52 mm Hg (range, 0.1 to 1.4 mm Hg) and 4 of the 5 patients had $PmO_2 < 1$ mm Hg. The tourniquet ischemia PmO_2 was reached at a mean of 15 minutes (range, 10 to 21 min) after tourniquet use.

After deflation of the tourniquet, a rapid increase in PmO_2 was observed to a peak value exceeding the pretourniquet PmO_2, which was ascribed to the hyperemic response. After the peak value, the PmO_2 decreased toward the pretourniquet PmO_2. The mean postdeflation peak PmO_2 was 94.68 mm Hg (range, 31.3-275 mm Hg) and was attained at a mean 12 minutes (range, 4-20.5 min) after tourniquet deflation.

Tibia Fracture

Eleven patients were included (Table 1). The mean age was 40.2 years (range, 25-83 y). None of the 11 patients developed compartment syndrome postoperatively. This assessment was based on a normal sensorimotor examination of the lower extremity, adequate pain control on oral medication, and ability to mobilize adequately for discharge from the hospital. These patients were followed postoperatively in the orthopedic clinic and none had physical examination evidence of a missed compartment syndrome. Qualitative analysis of postoperative PmO_2 revealed no apparent reproducible pattern.

TABLE 1. Demographic Data

Patient	Age	Sex	Surgery	Mechanism	TI Time
Control					
1	29	F	ORIF bimal/ syndes	Torsional injury	1 h 54 min
2	49	F	ORIF lat mal	Torsional injury	74 min
3	35	F	ORIF lat mal	Torsional injury	70 min
4	24	M	ORIF lat mal	Torsional injury	71 min
5	60	F	ORIF lat mal	Torsional injury	76 min
Experimental					
1	28	M	Tibial IMN	Torsional injury	—
2	46	F	Tibial IMN	PVA	—
3	38	M	Tibial IMN	Assault	—
4	28	M	Tibial IMN	PVA	—
5	36	M	Tibial IMN	MCA	—
6	33	M	Tibial IMN	Assault	—
7	25	M	Tibial IMN	Assault	—
8	33	M	Tibial IMN	BVA	—
9	53	M	Tibial IMN	Torsional injury	—
10	83	F	Tibial IMN	PVA	—
11	40	F	Tibial IMN	MCA	—

Bimal/sydnes indicates bimalleolar/syndesmosis; BVA, bicycle versus automobile; F, female; IMN, intramedullary nailing; lat mal, lateral malleolus; M, male; MCA, motorcycle accident; ORIF, open reduction internal fixation; PVA, pedestrian versus automobile.

All patients underwent intramedullary nailing of the tibia under anesthesia an FiO_2 (fraction of inspired air) of 50% was requested. The average well leg mean PmO_2 was 30.45 mm Hg (Table 2). The mean duration of total postoperative PmO_2 monitoring was 38.34 hours (range, 14.62-58.02 h). The average injured leg mean PmO_2 was 27.24 mm Hg. There was no significant difference in the PmO_2 means between the well leg and the injured leg ($P = 0.8$).

Warning Criteria

$PmO_2 < 10$ mm Hg

Of 11 patients, totaling 52,198 measurements spanning 424 hours, measurements meeting the prospective warning criterion were obtained in 2 patients for 178 minutes (7.46%) and 167 minutes (6.98%), respectively (Table 2). The mean duration of PmO_2 monitoring was 38.34 hours. Of the measurements < 10 mm Hg in the 2 patients, the lowest quartile PmO_2 were 8.94 and 8.03 mm Hg, respectively, indicating that a substantial decrease below 10 mm Hg did not occur.

DISCUSSION

In this prospective observational study, we established the safety and feasibility of using a minimally invasive probe for direct measurement of tissue oxygenation in human leg muscle. The probe was sensitive and rapidly responsive to skeletal muscle ischemia and reperfusion as demonstrated in tourniquet-induced arterial ischemia. A floor PmO_2 value of nearly zero was established in live ischemic muscle. In the postoperative period after tibia fracture surgery, continuous

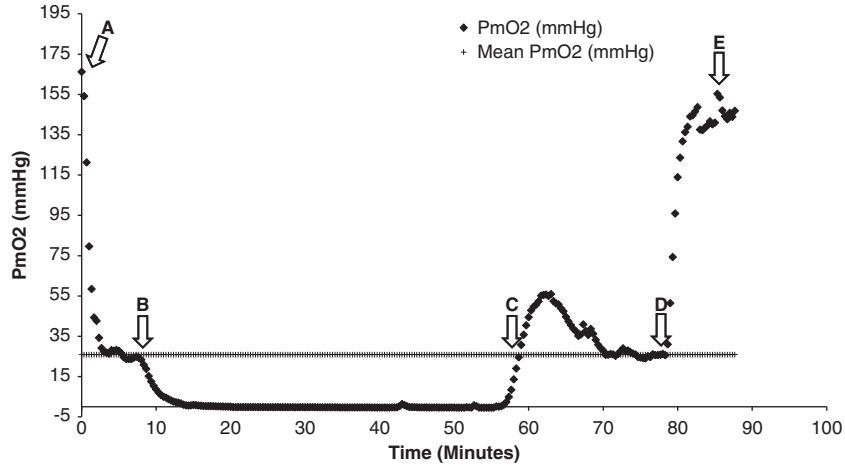

FIGURE 4. Continuous measurement of PmO_2 in the anterior compartment during tourniquet ischemia. The tissue oxygenation probe is calibrated to room air (154 mm Hg) before insertion into the leg (A). Upon insertion, PmO_2 equilibrates within the muscle (mean PmO_2). With the use of tourniquet (B), there is a rapid decrease to a substantially lower PmO_2. With the release of the tourniquet, there is a rapid increase in PmO_2 exceeding the pretourniquet value (C) to a posttourniquet peak, followed by normalization toward the pretourniquet PmO_2 (D). After removal, the value returned to room air (E). A highly similar pattern was exhibited in all 5 patients in the control arm.

monitoring of tissue oxygenation was possible for a prolonged duration and seemed to show a low false-positive rate, that is, only 1.35% of PmO_2 measurements spanning 424 hours fulfilled the warning criterion in the absence of compartment syndrome.

Timely and accurate diagnosis of acute compartment syndrome remains one of the major unsolved clinical problems in orthopedic surgery. Although it is currently considered a clinical diagnosis, the use of objective data is often necessary in settings where a reliable clinical examination is either impossible or equivocal. To date, direct measurement of compartment pressure remains the primary objective method of diagnosing compartment syndrome, but there is considerable controversy regarding the pressure threshold for performing fasciotomy. Tissue oxygenation may be a more accurate indicator of the pathophysiology of compartment syndrome, specifically muscle ischemia and necrosis.

Compartment pressure has been reported to have poor specificity, and reliance on this modality may lead to excessive fasciotomy. Janzing and Broos[5] monitored pressure in 95 patients after tibial fracture and found that adherence to the warning criterion of $\Delta P < 30$ mm Hg would have resulted in a theoretical fasciotomy rate of 45%, compared with the actual rate of 14%. They concluded that a reliable threshold pressure could not be determined. Findings such as these explain the preference of many surgeons to avoid continuous pressure monitoring due to the concern that high values will obligate them to perform unnecessary fasciotomy in the absence of compartment syndrome. Fasciotomy itself carries risks, including the morbidity of an invasive procedure, damage to neurovascular structures, infection, scarring, need for skin grafting surgery, and unsightly cosmesis.

Because the pathophysiology of compartment syndrome involves pressure-induced ischemia of muscle, monitoring tissue oxygenation as a strategy for diagnosing compartment syndrome makes good intuitive sense. Recently, studies of tissue oxygenation for the diagnosis of compartment syndrome have primarily focused on technology using NIRS.[6,7,19] This technology utilizes the differential light absorption properties of oxygenated and deoxygenated hemoglobin in the

TABLE 2. Tissue Oxygenation (PmO_2) After Tibia Fracture

Patient	Well Leg Mean PmO_2	n	Injured Leg PmO_2 Time hh:mm:ss	Mean PmO_2	n	Median PmO_2	Lowest 5%	Highest 5%	$PmO_2 < 10$ (n)	$PmO_2 < 10$ (min)
1	32.50	23	39:57:00	20.35	4770	20.83	9.53	36.18	356	178
2	13.72	194	38:59:00	29.27	6828	29.28	23.93	34.27	0	0
3	73.62	120	40:29:00	26.77	4740	25.63	18.22	38.37	0	0
4	52.70	425	40:36:00	26.60	4815	26.78	20.39	32.49	0	0
5	23.24	155	50:46:00	44.17	5632	46.89	23.95	54.98	0	0
6	22.84	113	46:20:00	25.11	5453	24.86	14.80	35.42	0	0
7	21.71	201	58:01:00	19.32	6928	19.43	15.07	24.07	0	0
8	26.16	318	39:57:00	24.74	4769	24.90	9.23	39.91	333	167
9	22.56	336	38:41:00	30.75	4613	30.99	25.38	35.99	0	0
10	19.74	146	15:56:30	31.02	1913	34.73	16.11	45.79	0	0
11	26.13	23	14:37:00	21.57	1737	22.29	14.14	26.10	0	0

PmO_2 (in mm Hg) was measured in the anterior compartment after intramedullary nailing and recorded every 30 seconds. The number and duration of measurements meeting the PmO_2 warning criterion are shown. PmO_2, partial pressure of oxygen in muscle.

microcirculation, is measured transcutaneously (noninvasively), and expresses results as a percentage of oxygenated/ deoxygenated hemoglobin (StO2).

In contrast, the tissue oxygen probe described in our technique utilizes a minimally invasive flexible polyethylene catheter for insertion and expresses results as the partial pressure of oxygen within the tissue (PmO_2). The probe provides a continuous, real time, direct measurement of PmO_2 in muscle and has been used in basic science and clinical studies. Troitzsch et al[20] placed the probe in the latissimus dorsi muscle in a rabbit model and found that PmO_2 responded rapidly to ischemia and correlated with markers of muscle ischemia including phosphocreatine, adenosine triphosphate, and intracellular pH. Another animal study found that PmO_2 was responsive to ischemia-reperfusion after ligation and release of the aorta and that prophylactic fasciotomy led to higher values of PmO_2 upon reperfusion.[21] The probe has been investigated on a small scale by plastic surgeons to monitor blood flow in free muscle flaps.[11] Kamolz and colleagues used continuous tissue oxygenation monitoring for 7 days in 60 free flaps. In 8 flaps with vascular compromise, a decrease in oxygenation was observed in all cases.[12] As the pathophysiology of compartment syndrome has significant differences from pure ischemia either from flap failure or vascular ligation, application of these results to compartment syndrome resulting from extremity trauma must be carried out with caution.

The warning criterion of $PmO_2 < 10$ mm Hg is a value suggested by previous investigators.[12,13] Of the 11 patients in the experimental arm of this study, PmO_2 measurements meeting this warning criterion occurred in only 2 patients for 178 minutes (7.46%) and 167 minutes (6.98%), respectively. Of the measurements < 10 mm Hg, the lowest quartile PmO_2 were 8.94 mm Hg and 8.03 mm Hg, respectively, indicating that a substantial decrease below 10 mm Hg did not occur. Because none of our patients developed clinically apparent compartment syndrome, it follows that skeletal muscle oxygenation was maintained above a critical threshold for irreversible ischemia. However, 10 mm Hg is ultimately an arbitrarily selected warning criterion. The additive effects of tissue trauma from the original injury and elevated compartment pressure may increase the oxygen requirement of leg muscle higher to avoid necrosis, that is, the PmO_2 threshold may actually be higher.

Direct measurement of the PmO_2, as performed in this study, has significant differences from NIRS. NIRS probes are transcutaneous, and therefore, their measurements are prone to variability due to soft tissue edema and skin turgor changes after trauma that alter the depth of the muscle to be evaluated and the ability of the probe to maintain its target. It is difficult to measure the deep posterior compartment of the leg with NIRS due to its anatomic location.[7] In contrast, the probe used in this study is inserted directly into the muscle where it remains. NIRS measures the percentage of oxygenated hemoglobin, which does not account for other factors (eg, hematocrit) that can affect oxygen delivery, whereas the probe used in this study reflects the actual PmO_2 present within tissue. A further limitation of the transcutaneous technique is the significant effect of skin pigmentation on the variability of NIRS values. Shuler and colleagues reported that black or darker pigmented subjects had mean values 9% lower than lighter pigmented subjects, which is a magnitude similar to the difference reported between ischemic compartments and uninjured contralateral legs in another study by the same authors.[7,19] It should also be noted that no threshold values of NIRS as warning criteria for compartment syndrome have been proposed as yet. In a clinical study using NIRS in patients diagnosed with acute compartment syndrome and treated with fasciotomy, Giannotti et al[6] reported statistically significant lower mean StO_2 before fasciotomy; however, in nearly 25% of the compartment syndrome patients, StO_2 was within the normal range, and vice versa, several of the control patients had StO_2 in the range of compartment syndrome values. The variability, indirect nature of hemoglobin saturation, and the lack of a clear effect size or threshold for ischemia limit the clinical applicability of NIRS as a method to diagnose compartment syndrome.

The strengths of our feasibility study include the duration and truly continuous nature of measurements. Tissue oxygenation data were collected for a mean 38 hours postoperatively, rather than minutes,[6,7,19] which allowed a thorough analysis of postoperative PmO_2 over time. As a pilot study of a novel method, this study has several inherent weaknesses. The number of patients is small. The narrow inclusion criteria limited enrollment. No compartment syndrome occurred, and therefore, no comparison could be made. A large number of patients would likely require enrollment before this relatively infrequent event occurs. Because the instruments and devices were not designed for this purpose, the experimental setup was extremely tedious and labor intensive. However, it is noteworthy that a predefined PmO_2 threshold (< 10 mm Hg) did seem to demonstrate a low false-positive rate relative to compartment pressure, which is the main objective test currently in use. Continuous measurement of tissue oxygenation was feasible, responsive, and had a floor value approximating zero. These factor favorably when considering the clinical applicability of this approach.

Future directions include large animal experiments that allow for induction of compartment syndrome under controlled conditions to investigate PmO_2 and establish clinically translatable thresholds of time and severity for reversible and irreversible necrosis. Concomitant measurement of compartment pressure would allow comparison of the proportion of measurements meeting the warning criteria. The probes were well tolerated. Expansion of indications to other locations (eg, forearm, intra-articular fractures), injuries (eg, open fractures, crush), and patients (eg, multiply injured, obtunded) would allow larger numbers of patients to be observed. This experience would be prerequisite to any consideration of clinical use.

We showed that tissue oxygenation was responsive to ischemia and generally remained above a predefined threshold of 10 mm Hg in the absence of compartment syndrome. The ultimate goal of our work is to study the continuous measurement of tissue oxygenation in muscle as a sensitive, objective, and physiologic method for the identification of acute compartment syndrome, on the basis of the rationale that the pathophysiology involves pressure-induced ischemia. As a direct indicator of the state of underlying muscle, it opens the door for further study of the indications and timing of fasciotomy and potential treatment alternatives, such as medical therapeutics that enhance oxygen delivery or decrease compartmental pressure.

ACKNOWLEDGMENTS

The authors thank Geoffrey Manley, MD, PhD, and Diane Morabito, RN, MPH (UCSF Department of Neurosurgery), Peggy Knudson, MD (UCSF Department of General Surgery), and Claude Hemphill III, MD (UCSF Department of Neurology) for their expertise, gracious assistance, and provision of

equipment necessary to execute this study, and Rajesh Jaganath, MD, for research support.

REFERENCES

1. McQueen MM, Christie J, Court-Brown CM. Acute compartment syndrome in tibial diaphyseal fractures. *J Bone Joint Surg Br*. 1996;78:95–98.
2. Kosir R, Moore FA, Selby JH, et al. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. *J Trauma*. 2007;63:268–275.
3. McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression. *J Bone Joint Surg Br*. 1996;78:99–104.
4. Willis RB, Rorabeck CH. Treatment of compartment syndrome in children. *Orthop Clin North Am*. 1990;21:401–412.
5. Janzing HM, Broos PL. Routine monitoring of compartment pressure in patients with tibial fractures: beware of overtreatment! *Injury*. 2001;32:415–421.
6. Giannotti G, Cohn SM, Brown M, et al. Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. *J Trauma*. 2000;48:396–399; discussion 9–401.
7. Shuler MS, Reisman WM, Whitesides TE Jr, et al. Near-infrared spectroscopy in lower extremity trauma. *J Bone Joint Surg Am*. 2009;91:1360–1368.
8. Greif R, Akca O, Horn EP, et al. Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med*. 2000;342:161–167.
9. Ikossi DG, Knudson MM, Morabito DJ, et al. Continuous muscle tissue oxygenation in critically injured patients: a prospective observational study. *J Trauma*. 2006;61:780–788; discussion 8–90.
10. Levy B, Gibot S, Franck P, et al. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*. 2005;365:871–875.
11. Hirigoyen MB, Blackwell KE, Zhang WX, et al. Continuous tissue oxygen tension measurement as a monitor of free-flap viability. *Plast Reconstr Surg*. 1997;99:763–773.
12. Kamolz LP, Giovanoli P, Haslik W, et al. Continuous free-flap monitoring with tissue-oxygen measurements: three-year experience. *J Reconstr Microsurg*. 2002;18:487–491; discussion 92–93.
13. Hofer SO, Timmenga EJ, Christiano R, et al. An intravascular oxygen tension monitoring device used in myocutaneous transplants: a preliminary report. *Microsurgery*. 1993;14:304–309; discussion 10–11.
14. Paek R, Chang DS, Brevetti LS, et al. Correlation of a simple direct measurement of muscle pO(2) to a clinical ischemia index and histology in a rat model of chronic severe hindlimb ischemia. *J Vasc Surg*. 2002;36:172–179.
15. Raittinen L, Laranne J, Baer G, et al. How we do it: postoperative tissue oxygen monitoring in microvascular free flaps. *Clin Otolaryngol*. 2005;30:276–278.
16. Sheridan GW, Matsen FA 3rd. Fasciotomy in the treatment of the acute compartment syndrome. *J Bone Joint Surg Am*. 1976;58:112–115.
17. Boekstegers P, Weidenhofer S, Pilz G, et al. Peripheral oxygen availability within skeletal muscle in sepsis and septic shock: comparison to limited infection and cardiogenic shock. *Infection*. 1991;19:317–323.
18. Bylund-Fellenius AC, Walker PM, Elander A, et al. Energy metabolism in relation to oxygen partial pressure in human skeletal muscle during exercise. *Biochem J*. 1981;200:247–255.
19. Shuler MS, Reisman WM, Kinsey TL, et al. Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. *J Bone Joint Surg Am*. 2010;92:863–870.
20. Troitzsch D, Vogt S, Abdul-Khaliq H, et al. Muscle tissue oxygen tension and oxidative metabolism during ischemia and reperfusion. *J Surg Res*. 2005;128:9–14.
21. Seekamp A, Van Griensven M, Blankenburg H, et al. Intramuscular partial oxygen tension monitoring in compartment syndrome—an experimental study. *Eur J Emerg Med*. 1997;4:185–192.

Injury, Int. J. Care Injured 44 (2013) 1076–1080

Contents lists available at SciVerse ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Comparison of tissue oxygenation and compartment pressure following tibia fracture

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ARTICLE INFO

Article history:
Accepted 10 November 2012

Keywords:
Acute compartment syndrome
Ischaemia
Tibia fracture
Tissue oxygenation
Trauma
Intramedullary nailing
Perfusion pressure
Compartment pressure
PmO_2
Fasciotomy

ABSTRACT

Objective: We investigated the ability of direct continuous measurement of intramuscular tissue oxygenation (PmO_2) to detect acute ischaemia in the leg in patients at risk for acute extremity compartment syndrome. Following tibia fracture treated by intramedullary nailing, we compared the proportions of PmO_2 and compartment pressure (CP) measurements that met the warning criteria for compartment syndrome.

Methods: Participants included 10 patients sustaining acute isolated closed tibia shaft fractures treated by intramedullary nailing. A tissue oxygenation probe and a CP probe were percutaneously placed into the anterior compartment of the leg. PmO_2 and CP in the anterior compartment were measured in the injured leg for 48 h postoperatively. Measurements meeting the warning criteria were defined as $PmO_2 < 10$ mmHg, CP > 30 mmHg and perfusion pressure $\Delta P < 30$ mmHg.

Results: None of the patients developed compartment syndrome. Comparison of CP and PmO_2 showed a CP > 30 mmHg in 50.39% of CP measurements in all patients and a $PmO_2 < 10$ mmHg in 0.75% of PmO_2 measurements in two patients ($P = 0.005$). Comparison of ΔP and PmO_2 showed a $\Delta P < 30$ mmHg in 31.01% of ΔP measurements in nine patients and a $PmO_2 < 10$ mmHg in 0.76% of PmO_2 measurements in one patient ($P = 0.01$).

Conclusion: In the absence of compartment syndrome, pressure measurements following tibia fracture treated with intramedullary nailing often met the warning criteria, whereas PmO_2 did not, suggesting that measurement of intramuscular tissue oxygenation may represent a potential method for the identification of acute compartment syndrome that deserves continued investigation.

Introduction

Acute compartment syndrome describes the elevation of pressure within the non-yielding fascial compartments of the extremities, leading to compromise of circulation, local ischaemia and ultimately tissue necrosis. This is a potentially devastating sequela of tibia fracture.[1,2] Delay in diagnosis or treatment may have catastrophic consequences; therefore, timely and accurate diagnosis is imperative. The main objective test in current use is measurement of compartment pressure (CP). However, considerable controversy exists with regard to thresholds for fasciotomy,[3,4] which has resulted in problematic clinical ambiguity.

Because the pathophysiology of compartment syndrome involves pressure-induced ischaemia of muscle, monitoring tissue oxygenation represents a potential method for diagnosis. Use of an intramuscular probe to directly measure the partial pressure of oxygen may represent one strategy of assessing tissue oxygenation. The probe used in this study is a polarographic oxygen probe approved for monitoring brain tissue in the intensive care setting.[5] It has also been studied for applications within skeletal muscle and has been found to be highly responsive to changes in tissue oxygenation.[6–8] Continuous measurement of tissue oxygenation has been shown to be feasible in leg muscle in humans following tibia fracture.[9] A partial pressure of oxygen <10 mmHg has been suggested as a possible threshold for irreversible muscle ischaemia.[10,11]

The purpose of this study is to simultaneously record CP and intramuscular tissue oxygenation (PmO_2) in a cohort of patients deemed at risk for compartment syndrome and to compare the proportion of measurements meeting pre-defined warning criteria for compartment syndrome. We hypothesised that a considerable

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0020–1383/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.injury.2012.11.012

percentage of postoperative CP measurements would meet established warning criteria for compartment syndrome, consistent with the literature, whereas PmO_2 measurements would not meet the warning criteria for irreversible ischaemia in the absence of compartment syndrome.

Patients and methods

This study was approved by the institutional review board (approval H50856-32886-01) and written informed consent was received from all enrolled patients. This was designed as a prospective observational study. We chose to study the anterior compartment of the leg because it is most frequently affected by compartment syndrome.[1,12] The cohort consisted of patients who underwent surgery for a tibia fracture with intramedullary nailing. Continuous measurement of PmO_2 and CP was performed postoperatively.

Inclusion criteria were: age $\geq$18 years, admission via the Emergency Department, unilateral isolated closed acute tibia shaft fracture and minimum 6 h of concurrent measurement of PmO_2 and CP or ΔP. Exclusion criteria were: inability to give consent due to intoxication or head injury, open fracture, bilateral tibia fractures, tibia plateau or plafond fracture, ipsilateral femur or pelvis fracture, impending/established acute compartment syndrome or refusal to participate. Bilateral injuries were excluded because it precluded the ability to obtain control data from the contralateral limb. Open fractures were excluded because of the potential difficulty in placing the probes percutaneously without violating open wounds and risking contamination. Only tibial shaft fractures amenable to intramedullary nail fixation were included to avoid the surgical incisions necessary for open reduction internal fixation.

The tissue oxygenation probe used (Licox Combined Oxygen and Temperature Probe CC1.P1, Integra, Plainsboro, NJ, USA) is a Clark type polarographic oxygen probe and temperature measurement system that uses an electrochemical micro-cell for oxygen sensing, expressed as the partial pressure of oxygen (PmO_2). The CP probe used (Synthes Compartment Pressure Monitoring System, Synthes, Inc., West Chester, PA, USA) is a multi-use electronic transducer tipped catheter.[13] Both probes were placed percutaneously into the anterior compartment of the leg under sterile conditions using a Seldinger technique.[14] Detailed description of probe placement technique has been previously reported.[9] The probes were connected to a computer for data recording, which was maintained in a locked box at the patient's bedside.

Both the injured and the healthy legs underwent sterile surgical preparation and draping. The tissue oxygenation probe and the CP probe were placed in the uninjured (healthy) leg while under anaesthesia. PmO_2 and CP were recorded continuously from the healthy leg while intramedullary nailing was performed on the contralateral injured leg. After surgery was completed, sterile conditions were maintained, and both probes were removed from the healthy leg and placed in the injured leg. A sterile band-aid was placed over the probe insertion sites on the injured leg. The injured leg was then placed in a removable walking boot.

While the tissue oxygenation probe could be disconnected from the recording device as needed for patient mobilisation and subsequently re-connected, the pressure probe did not have this capability. Therefore, CP monitoring ended when the patient was mobilised. At the conclusion of the data collection period, the probes were removed from the patient and a sterile band-aid was placed over the probe insertion sites on the injured leg.

CP and PmO_2 were measured continuously and recorded every 2 min. In some patients, data were recorded every 30 s, and in these cases all data were included for all analysis. Measurement began 15 min after insertion of the tissue oxygenation probe to allow time for calibration. After surgery was completed, the pressure and tissue oxygenation probes were placed in the injured leg and measurements were recorded in the same fashion. Continuous monitoring of PmO_2 and CP was performed for up to 48 h postoperatively, except during transport and physical therapy. The patient and treating nurses and physicians were blinded to the PmO_2 and CP measurements, which were contained in a locked box at the patient's bedside.

Warning criteria

The number of measurements meeting prospectively defined warning criteria for compartment syndrome was based on previously published studies: absolute intracompartmental pressure (CP) >30 mmHg,[15,16] perfusion pressure (ΔP = diastolic blood pressure – CP) <30 mmHg[4] and tissue oxygenation (PmO_2) <10 mmHg.[11,17] The number of measurements meeting the tissue oxygenation warning criterion ($PmO_2 < 10$ mmHg) was compared with the number of measurements meeting the warning criteria for CP and ΔP. Blood pressure measurements made in the early postoperative patient were occasionally not accessible for recording. This resulted in shorter durations of ΔP measurements compared to PmO_2 and CP.

Statistical analysis

Descriptive statistics were used to describe PmO_2 and CP measurements (mean, median, 5th–95th percentiles). Because of the large number of measurements recorded for each patient, the pooled means of PmO_2 and CP of the healthy leg and the injured leg were compared using Wilcoxon ranked sums test for paired data. The proportion of measurements meeting prospectively defined warning criteria were calculated and compared for PmO_2 and CP or ΔP using Wilcoxon ranked sums test for paired data.

Results

The experimental arm consisted of 10 patients (7 male, 3 female). Mean age was 40.5 years (range, 25–83 years). The mechanism of injury was: motor vehicle accident ($n = 3$), pedestrian versus automobile ($n = 3$), assault ($n = 2$) and torsional injury ($n = 2$). Probes were well tolerated. No probe-related complications occurred. None of the 10 patients developed compartment syndrome postoperatively. This assessment was based on a normal sensorimotor exam of the lower extremity, adequate pain control on oral medication and ability to mobilise adequately for discharge from the hospital. These patients were followed postoperatively in the orthopaedic clinic and none had physical exam evidence of a missed compartment syndrome.

All patients underwent intramedullary nailing of the tibia under anaesthesia. The average healthy leg mean PmO_2 was 30.45 mmHg and average injured leg mean PmO_2 was 27.24 mmHg; the difference between the healthy and injured legs was not statistically significant ($P = 0.08$). The average healthy leg mean CP (measured in nine patients) was 17.19 mmHg and the average injured leg mean CP was 30.67 mmHg; the difference between the healthy and injured legs was statistically significant ($P = 0.02$). The mean duration of CP measurements was 33.35 h, while the mean duration of ΔP measurements ($n = 9$ eligible) was 27.8 h.

Qualitative analysis of postoperative PmO_2 data revealed no appreciably reproducible pattern. In 8 of 10 patients, CP appeared to be highest immediately postoperatively and then gradually decreased over time. Statistically significant correlations ($P < 0.001$) between PmO_2 and CP were found in all cases, with Pearson correlation coefficients ranging from −0.720 to 0.585 (Fig. 1). The coefficient was negative in eight patients, indicating an

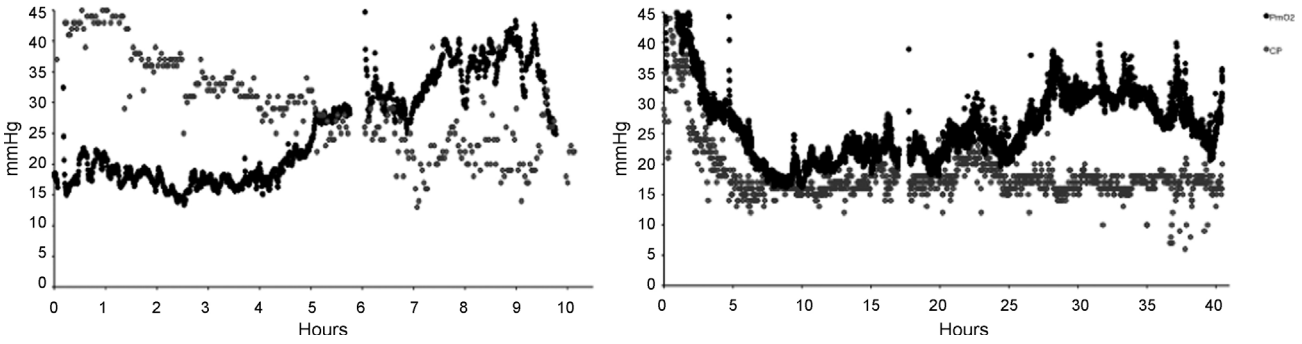

Fig. 1. Recordings of CP and PmO_2 measurements from two patients demonstrating lack of uniform correlation between CP and PmO_2. Left: inverse relationship observed (negative correlation) between CP and PmO_2 post intramedullary nailing. CP appears to decrease as PmO_2 increases. Right: positive relationship (positive correlation) between CP and PmO_2 post intramedullary nailing. CP and PmO_2 appear to parallel each other.

Table 1
$PmO_2 < 10$ mmHg versus CP > 30 mmHg: proportion of concurrent PmO_2 and CP measurements meeting warning criteria. Difference in proportions meeting warning criteria was significant ($P = 0.005$). Includes only measurements for which CP and PmO_2 were both recorded.

Patient	Injured leg hh:mm:ss	*n*	Mean CP	Mean PmO_2	% CP > 30	% PmO_2 < 10	Pearson correlation coefficient
1	28:42:00	861	27.76	22.28	22.65%	0.58%	−0.451
2	19:59:00	590	33.30	30.20	69.83%	0.00%	0.11
3	40:29:00	4670	18.17	26.75	3.81%	0.00%	0.585
4	18:08:00	537	28.82	25.18	68.53%	0.00%	−0.195
5	33:08:00	994	32.60	45.43	37.49%	0.00%	−0.423
6	46:20:00	1357	48.86	25.12	99.85%	0.00%	−0.673
7	58:01:00	1567	28.70	19.14	31.72%	0.00%	−0.267
8	39:57:00	1186	29.86	24.78	39.21%	6.91%	−0.173
9	38:41:00	1141	37.59	30.76	85.10%	0.00%	−0.41
10	10:08:00	278	29.85	25.24	45.68%	0.00%	−0.72

inverse relationship between PmO_2 and CP measurements, and positive in two, indicating a positive relationship. The two patients with positive correlation coefficients had PmO_2 measurements that paralleled CP in the early postoperative period, with both displaying high values immediately postoperatively that subsequently decreased over time.

Warning criteria

$PmO_2 < 10$ mmHg versus CP > 30 mmHg (Table 1). All 10 patients eligible for comparison had measurements meeting the warning criterion of CP > 30 mmHg in the absence of compartment syndrome, with a mean of 50.39% (range, 3.81–99.85%) of measurements meeting this warning criterion. Concurrent PmO_2 measurements meeting the warning criterion of $PmO_2 < 10$ mmHg occurred in two patients for a mean of 0.75% of measurements. The difference in the proportions of PmO_2 and CP meeting warning criteria was statistically significant ($P = 0.005$).

$PmO_2 < 10$ mmHg versus $\Delta P < 30$ mmHg (Table 2). Eight of 9 patients eligible for comparison had measurements meeting the warning criterion of $\Delta P < 30$ mmHg in the absence of compartment syndrome, with a mean of 31.01% (range, 0.28–97.68%) of measurements. Concurrent PmO_2 measurements meeting the warning criterion of $PmO_2 < 10$ mmHg occurred in one patient for a mean of 0.76% of measurements. The difference in proportions of PmO_2 and ΔP meeting warning criteria was statistically significant ($P = 0.01$).

Exclusion of early postoperative period

Because the high CP observed in the early postoperative period may have produced misleading results, data obtained during the first 3 h of monitoring in the injured leg were analysed separately. CP during the first 3 h was significantly higher than the subsequent postoperative measurements in eight patients, significantly lower in one patient and not significantly different

Table 2
$PmO_2 < 10$ mmHg versus $\Delta P < 30$ mmHg: proportion of concurrent PmO_2 and ΔP measurements meeting warning criteria. Difference in proportions meeting warning criteria was significant ($P = 0.01$). Includes only measurements for which ΔP and PmO_2 were both recorded. Fewer ΔP values were available compared to CP because of missing BP; PmO_2 values at time points without ΔP values were excluded.

Patient	Injured leg hh:mm:ss	*N*	Mean ΔP	Mean PmO_2	% $\Delta P < 30$	% $PmO_2 < 10$
1	24:22:00	656	43.32	24.00	3.81%	0.00%
2	19:59:00	590	45.30	30.20	23.39%	0.00%
3	14:51:00	1762	40.02	29.69	0.28%	0.00%
4	14:28:00	417	27.91	24.94	78.18%	0.00%
5	33:08:00	995	34.52	45.42	31.86%	0.00%
6	42:29:00	1249	17.46	26.01	97.68%	0.00%
7	24:40:00	738	62.43	20.17	0.00%	0.00%
8	38:53:00	1156	42.48	25.03	6.92%	6.83%
9	37:30:00	1107	35.32	31.02	37.01%	0.00%

in one patient. Correlations between PmO_2 and CP excluding the first 3 h resulted in Pearson correlation coefficients ranging from −0.662 to 0.280. The coefficient was significant and negative in seven patients, significant and positive in one and not significant in two. The proportion of measurements meeting warning criterion of $\Delta P < 30$ was not considerably affected by the first 3 h postoperative; only four of nine patients had ΔP calculated in this period (due to absent DBP recording), during which the mean proportion of $\Delta P < 30$ was 26.9%.

Discussion

The safety and feasibility of using a minimally invasive probe for direct measurement of tissue oxygenation in the anterior compartment of the leg in humans have been previously reported; results of PmO_2 measurements during tourniquet-induced ischaemia demonstrated that the probe was sensitive and rapidly responsive to skeletal muscle ischaemia and reperfusion. A floor PmO_2 value of nearly 0 mmHg was established in live ischaemic muscle.[9] For the current study, the clinical setting was the postoperative period following tibia fracture surgery. Although the frequency of compartment syndrome in the postoperative period is considered lower than in the time around injury, it remains a known risk of intramedullary nailing.[18,19] More common utilisation of regional anaesthesia and patient-controlled analgesia make this complication increasingly relevant in current practice.[20,21]

The current study demonstrates that, in the setting of recent fracture and intramedullary nailing, continuous monitoring of tissue oxygenation was possible for a prolonged duration and appeared to show a lower false positive rate than CP. Less than 1% of all PmO_2 measurements spanning 333 h of monitoring met the warning criterion in the absence of compartment syndrome, compared to 37.5% of all CP and 29.1% of all ΔP measurements showing elevated pressures. Measurements meeting the PmO_2 warning criteria were rare and brief. As expected, ΔP appeared to display a lower false positive rate than CP.

The postoperative CP and ΔP results are consistent with previous reports noting poor specificity of these measurements. Janzing and Broos monitored pressure in 95 patients after tibia fracture and found that adherence to warning criterion of $\Delta P < 30$ mmHg would have resulted in a theoretical fasciotomy rate of 45%, compared to the actual rate of 14%.[3] Following tibia fracture, 100% of our patients had measurements meeting the warning criterion of CP exceeding 30 mmHg, and eight of nine patients had measurements meeting the criterion of $\Delta P < 30$ mmHg. The difference in results may be explained by the truly continuous monitoring in the current study, in which CP was recorded every 30 s or 2 min, compared to 1 or 3 h in the above study. Findings such as these explain the reluctance of many surgeons to adopt routine CP monitoring due to concern that high CP values will obligate them to perform unnecessary fasciotomy in the absence of compartment syndrome.

It should be noted that our objectives did not include the study of PmO_2 in the setting of compartment syndrome. No compartment syndrome occurred, and therefore no comparison could be made. A large number of patients would be necessary to observe this relatively infrequent complication, and even more would be necessary to perform a statistically meaningful analysis. Use of fasciotomy as the 'gold standard' is also problematic because the decision to perform fasciotomy is often subjective. Indeed, it is conceivable that, should a patient in the study, where none of the patients developed compartment syndrome, for complaint of disproportionate pain during a period of elevated CP, a fasciotomy would have been performed. It is noteworthy that a pre-defined PmO_2 threshold (<10 mmHg) did appear to demonstrate a lower false positive rate than CP, which is the main objective test currently in use.

Because the pathophysiology of compartment syndrome involves pressure-induced ischaemia of muscle, tissue oxygenation as an approach to diagnosing compartment syndrome makes intuitive sense. Recently, studies of tissue oxygenation for diagnosis of compartment syndrome have primarily focussed on technology utilising near-infrared spectroscopy (NIRS).[22–24] NIRS utilises different technology, is measured transcutaneously (noninvasively) and expresses results as a percentage of oxygenated haemoglobin (StO_2). The variability, indirect nature of haemoglobin saturation and lack of a clear effect size or threshold for ischaemia have limited the clinical applicability of NIRS. In contrast, the tissue oxygen probe used in this study is invasive and utilises a microsensor that employs a red-ox reaction to determine PmO_2.

PmO_2 has been found to respond rapidly to ischaemia and correlate with biochemical markers of muscle ischaemia including phosphocreatine, adenosine triphosphate (ATP) and intracellular pH.[25] A $PmO_2 < 10$ mmHg has been suggested as a warning criterion based on normal values of skeletal muscle and the clinical experience of plastic surgeons who have investigated tissue oxygenation to monitor free muscle flaps. Hofer et al. reported that of 14 flaps, all 3 with $PmO_2 < 10$ mmHg exhibited clinical signs of circulatory compromise that were confirmed at re-operation.[10,11,26] This potential threshold is further supported by results collected using the same probe from the deltoid muscle of intensive care unit (ICU) patients (unpublished data provided by investigators at our institution); of 114,644 measurements in 26 patients, 0.5% were 11 mmHg or below, supporting the hypothesis that $PmO_2 < 10$ mmHg may be considered abnormal. Measurements meeting this warning criterion occurred in only two patients for <3 h. Because none of our patients developed clinically apparent compartment syndrome, it is likely that skeletal muscle oxygenation was maintained above a critical threshold for clinically important irreversible ischaemia.

Compared to the healthy legs, the injured legs demonstrated significantly higher CP while PmO_2 was not significantly different. The increase in pressure is likely due to inflammation, tissue trauma and oedema as a result of surgery. Statistically significant correlations between CP and PmO_2 were detected in all patients and were negative in eight but, somewhat unexpectedly, positive in two, indicating that CP and PmO_2 moved in parallel. The finding of statistically significant correlations is due in part to the large number of data points obtained for each patient. While it is tempting to hypothesise that CP and PmO_2 should move in opposite directions, since pressure is posited to induce ischaemia, the tissue conditions in muscle following trauma or surgery probably defy simple explanation. An alternative scenario is that the hyperaemic response to trauma or surgery to the leg may lead to an increase in CP and PmO_2. The increase in CP may be a reflection of blood flow to the muscle. Exclusion of the first 3 h postoperatively, when CP was higher than the rest of the postoperative period, did not substantially alter the results. The results support the conclusion that a complex interplay of factors determines PmO_2 in leg muscle following tibia fracture and therefore the assumption that increased pressure denotes decreased oxygen may sometimes be inaccurate. The results also suggest that CP may be a poor surrogate for the oxygenation status of the underlying muscle.

As a pilot study of a novel method, this study has several inherent weaknesses. The number of patients is small. Technical limitations of the pressure probe led to missing data. Systemic blood pressure used to calculate ΔP was measured infrequently, which may have affected the accuracy of the calculated ΔP. The narrow inclusion criteria limited enrolment. Similar to the

protocols of previous studies of CP,[4] only the anterior compartment was monitored; the anterior compartment was involved in 100% of cases of acute compartment syndrome in one large series.[27] The experimental set-up and available equipment also limited monitoring to a single compartment in one leg; hence, simultaneous monitoring of the injured and the healthy leg was not feasible postoperatively. Healthy-leg PmO_2 measurements obtained intra-operatively were consistent with previously reported normal values.[9,17]

The strengths of this study include the duration and continuous nature of measurements. Tissue oxygenation data were collected for a mean of 33 h postoperatively, rather than minutes,[22–24] which allowed a thorough analysis of postoperative PmO_2 over time. In contrast to other studies, CP, blinded to the treating providers, was also recorded continuously to allow for comparison with the currently used objective method. Future directions include large animal experiments that allow for induction of compartment syndrome under controlled conditions in order to investigate PmO_2 and correlate measurements with direct examination of muscle viability or necrosis. Expansion of indications to other locations (e.g., forearm and intra-articular fractures), injuries (e.g., open fractures and crush) and patients (e.g., multiply injured and obtunded) would allow larger numbers of patients to be observed. An interesting future case-control study would include measurement of PmO_2 in patients diagnosed with compartment syndrome, although this may be problematic for the reasons described above. The ultimate goal of our work is to study continuous measurement of tissue oxygenation in muscle as a specific, objective and physiologic method for the identification of acute compartment syndrome. As a direct indicator of the state of underlying muscle, it opens the door for further study of the indications and timing of fasciotomy, as well as potential treatment alternatives, perhaps including medical therapeutics that enhance oxygen delivery or decrease CP.

Conclusion

In this study, it has been shown that in the absence of compartment syndrome, pressure measurements following tibia fracture treated with intramedullary nailing often met warning criteria, whereas PmO_2 did not. Measurement of intramuscular tissue oxygenation was feasible in the clinical setting and may represent a more physiologic and specific method for diagnosis of acute compartment syndrome that merits continued investigation.

Disclosure

Erik Hansen received a grant from the OTA. Utku Kandemir received a grant from the Osteosynthesis and Trauma Care Foundation. James Mok receives grant support from the Department of Defense (DOD) Peer Reviewed Orthopaedic Research Program (PRORP). James Mok is an employee of the United States Army. The opinions and assertions herein are the private views of the author and are not to be construed as official or reflecting the views of the Department of Defense or the United States government.

Funding

This study was funded in part by an Orthopaedic Trauma Association resident research grant (ENH). None of the study sponsors were involved in the study design; collection, analysis and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript.

References

1. McQueen MM, Christie J, Court-Brown CM. Acute compartment syndrome in tibial diaphyseal fractures. *Journal of Bone and Joint Surgery British Volume* 1996;**78**:95–8.
2. Kosir R, Moore FA, Selby JH, Cocanour CS, Kozar RA, Gonzalez EA. Acute lower extremity compartment syndrome (ALECS) screening protocol in critically ill trauma patients. *Journal of Trauma* 2007;**63**:268–75.
3. Janzing HM, Broos PL. Routine monitoring of compartment pressure in patients with tibial fractures: beware of overtreatment. *Injury* 2001;**32**:415–21.
4. McQueen MM, Court-Brown CM. Compartment monitoring in tibial fractures. The pressure threshold for decompression. *Journal of Bone and Joint Surgery British Volume* 1996;**78**:99–104.
5. van den Brink W, Moos AR. Brain oxygen tension in severe head injury. *Neurosurgery* 2000;**46**:868–78.
6. Greif R, Akca O, Horn EP, Kurz A, Sessler DI, Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *New England Journal of Medicine* 2000;**342**:161–7.
7. Ikossi DG, Knudson MM, Morabito DJ, Cohen MJ, Wan JJ, Khaw L, *et al.* Continuous muscle tissue oxygenation in critically injured patients: a prospective observational study. *Journal of Trauma* 2006;**61**:780–8. discussion 788–90.
8. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na^+K^+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet* 2005;**365**:871–5.
9. Mok JM, Hansen EN, Kang H, Kandemir U. Diagnosis of acute compartment syndrome: direct measurement of tissue oxygenation. *Techniques in Orthopaedics* 2012;**27**:22–9.
10. Hirigoyen MB, Blackwell KE, Zhang WX, Silver L, Weinberg H, Urken ML. Continuous tissue oxygen tension measurement as a monitor of free-flap viability. *Plastic and Reconstructive Surgery* 1997;**99**:763–73.
11. Kamolz LP, Giovanoli P, Haslik W, Koller R, Frey M. Continuous free-flap monitoring with tissue-oxygen measurements: three-year experience. *Journal of Reconstructive Microsurgery* 2002;**18**:487–91. discussion 492–483.
12. Sheridan GW, Matsen 3rd FA. Fasciotomy in the treatment of the acute compartment syndrome. *Journal of Bone and Joint Surgery* 1976;**58**:112–5.
13. Willy C, Gerngross H, Sterk J. Measurement of intracompartmental pressure with use of a new electronic transducer-tipped catheter system. *Journal of Bone and Joint Surgery* 1999;**81**:158–68.
14. SI S. Catheter replacement of the needle in percutaneous arteriography: a new technique. *Acta Radiologica* 1953;**39**:368–76.
15. Mubarak SJ, Owen CA, Hargens AR, Garetto LP, Akeson WH. Acute compartment syndromes: diagnosis and treatment with the aid of the wick catheter. *Journal of Bone and Joint Surgery* 1978;**60**:1091–5.
16. Hargens AR, Schmidt DA, Evans KL, Gonsalves MR, Cologne JB, Garfin SR, *et al.* Quantitation of skeletal-muscle necrosis in a model compartment syndrome. *Journal of Bone and Joint Surgery* 1981;**63**:631–6.
17. Raittinen L, Laranne J, Baer G, Pukander J. How we do it: postoperative tissue oxygen monitoring in microvascular free flaps. *Clinical Otolaryngology* 2005;**30**:276–8.
18. Mawhinney IN, Maginn P, McCoy GF. Tibial compartment syndrome after tibial nailing. *Journal of Orthopaedic Trauma* 1994;**8**(3):212–4.
19. Tischenko GJ, Goodman SB. Compartment syndrome after intramedullary nailing of the tibia. *Journal of Bone and Joint Surgery* 1990;**72**(January (1)):41–4.
20. Hyder N, Kessler S, Jennings AG, De Boer PG. Compartment syndrome in tibial shaft fracture missed because of a local nerve block. *Journal of Bone and Joint Surgery British Volume* 1996;**78**(May (3)):499–500.
21. Harrington P, Bunola J, Jennings AJ, Bush DJ, Smith RM. Acute compartment syndrome masked by intravenous morphine from a patient-controlled analgesia pump. *Injury* 2000;**31**(June (5)):387–9.
22. Shuler MS, Reisman WM, Whitesides Jr TE, Kinsey TL, Hammerberg EM, Davila MG, *et al.* Near-infrared spectroscopy in lower extremity trauma. *Journal of Bone and Joint Surgery* 2009;**91**:1360–8.
23. Shuler MS, Reisman WM, Kinsey TL, Whitesides Jr TE, Hammerberg EM, Davila MG, *et al.* Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. *Journal of Bone and Joint Surgery* 2010;**92**:863–70.
24. Giannotti G, Cohn SM, Brown M, Varela JE, McKenney MG, Wiseberg JA. Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. *Journal of Trauma* 2000;**48**:396–9. discussion 399–401.
25. Troitzsch D, Vogt S, Abdul-Khaliq H, Moosdorf R. Muscle tissue oxygen tension and oxidative metabolism during ischemia and reperfusion. *Journal of Surgical Research* 2005;**128**:9–14.
26. Hofer SO, Timmenga EJ, Christiano R, Bos KE. An intravascular oxygen tension monitoring device used in myocutaneous transplants: a preliminary report. *Microsurgery* 1993;**14**:304–9. discussion 310–311.
27. McQueen MM, Gaston P, Court-Brown CM. Acute compartment syndrome. Who is at risk? *Journal of Bone and Joint Surgery British Volume* 2000;**82**(2):200–3.